

New and Novel Cyclisation Reactions of Imidoalkenes



William O'Neill, MChem

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Declaration

I declare that the work presented in this thesis was carried out by myself, unless otherwise stated by reference, and that it has not been previously submitted for any higher degree.

This thesis describes the results of research carried out in the research labs of Professor Hamish McNab in the department of chemistry at the University of Edinburgh

William John O'Neill
University of Edinburgh
April 2009

Abstract

The effect of scale on the conversion to products in flash vacuum pyrolysis experiments was studied using four model reactions. Overall, conversion was dependent on reaction scale up to 0.5 g, but above 0.5 g, the effect was minimal and within experimental error. This effect was shown to be due to variations in contact time of the molecules in the furnace tube. Altering the furnace tube diameter had the effect of increasing the conversion to product.

The pyrolysis of *ortho*-anilinomethylene Meldrum's acid derivatives was investigated. Typically the 8-substituted quinolin-4-one was obtained as the major product, with a few exceptions. Certain substituents (such as nitro) were found to react with the ketene produced in the reaction to give alternative products, while others (such as chloro- and *N*-unsubstituted amides) gave the 3-substituted quinolin-4-ones *via ipso*-cyclisation and migration of the substituent.

The regioselectivity of the pyrolysis of *meta*-anilinomethylene Meldrum's acid derivatives, to give 5- and 7-substituted quinolin-4-ones, was studied. In general a 3:1 – 4:1 ratio of regioisomers was obtained, in favour of the 7-substituted quinolin-4-one. Substituents capable of hydrogen bonding, such as hydroxy-, were shown to give the 5-substituted quinolin-4-one exclusively and DFT calculations were employed to show that, in these examples, the 5-substituted product was favoured energetically.

The pyrolysis of the methylene Meldrum's acid derivative of 3-aminophenol gave 8-hydroxyquinolizinone as the sole product at low temperatures, with 5-hydroxyquinolinone as the major product formed at higher temperatures. The mechanism involves a regioselective electrocyclisation, followed by a hydrogen transfer and generation of a new ketene. Cyclisation of this ketene gives the quinolizinone. The scope of this reaction was explored, with a number of derivatives synthesised, and substitution on the aminophenol and the ketene generator was tolerated. The reactivity of the quinolizinones was also explored. The hydroxy-group was found to be phenol-like and underwent similar reactions, such as alkylations and acetylations. The compound was found to be highly reactive towards electrophiles, reacting in the 1- and 3- positions of the ring system, often in both positions.

The pyrolysis of the aminomethylene Meldrum's acid derivatives of certain pyridazinones was shown to give pyridopyrazidinediones. In some examples, a

second product based on a pyrrolopyridazine ring system was observed and DFT calculations show that the mechanism involves probably an electrocyclisation, followed by a decarboxylation reaction.

Pyrolysis of amino acid ester derivatives of methylene Meldrum's acid were shown to give *N*-unsubstituted 3-hydroxypyrroles and 1*H*-pyrrol-3(2*H*)-ones. Different amino acids were tolerated in the reaction, as were different electron-withdrawing groups in place of the amino acid ester. DFT calculations were employed to explore the mechanism of the reaction. 3-Hydroxypyrrole was also synthesised from the pyrolysis of Meldrum's acid derivative of glycine *tert*-butyl ester, and the reactivity of the compound explored for the first time. The compound was found to be reactive towards electrophiles, such as diazonium salts, and could be *O*-acetylated under appropriate conditions.

Contents

Abbreviations	4
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Chapter 1 – Studies on the effect of scale on conversion in FVP experiments

1.1	Introduction	7
1.2	Discussion	8
1.2.1	Model Reaction 1: Pyrrolizinone Formation	9
1.2.2	Model Reaction 2: <i>E/Z</i> Double Bond Isomerisation	12
1.2.3	Model Reaction 3: De-Esterification	17
1.2.4	Overview	21
1.3	Conclusion	21
1.4	Experimental	23

Chapter 2 – Pyrolysis of *Ortho*-anilinomethylene Meldum's acid Derivatives under FVP Conditions

2.1	Introduction	31
2.2	Discussion	43
2.2.1	Mechanism of the Reaction	43
2.2.2	Pyrolysis of <i>Ortho</i> -anilinomethylene Meldum's acid Derivatives	49
2.2.2.1	Introduction	49
2.2.2.2	Synthesis of Starting Materials	51
2.2.2.3	Pyrolysis Experiments	52
2.2.2.4	Migratory Aptitudes of Substituents	79
2.3	Conclusion	80
2.4	Experimental	82

Chapter 3 – Pyrolysis of *Meta*-anilinomethylene Meldum's acid Derivatives under FVP Conditions

3.1	Discussion	106
3.1.1	Introduction	106
3.1.2	Synthesis of Starting Materials	107
3.1.3	Pyrolysis of <i>Meta</i> -anilinomethylene Meldum's acid Derivatives	111
3.1.4	Discussion of the Regioselectivity	113
3.1.5	Regioselectivity of Groups Capable of Hydrogen Bonding	116

3.1.6	Regioselectivity of <i>N</i> - or <i>O</i> -Acetylated Examples	121
3.1.7	DFT Rationale for the Regioselectivity	124
3.2	Conclusion	127
3.3	Experimental	128

Chapter 4 – Synthesis of 8-Hydroxyquinolizinones by FVP

4.1	Introduction	153
4.1.1	Synthesis of Quinolizinones	153
4.1.2	Synthesis of Hydroxyquinolizinones	160
4.1.3	Conclusion	169
4.2	Discussion	170
4.2.1	Synthesis of 8-Hydroxyquinolizinones	170
4.2.2	Mechanism	175
4.2.3	Alternative Routes to Pyridyl Ketenes	181
4.2.4	Solution Phase Pyrolysis	185
4.2.5	Scope of Reaction	186
	4.2.5.1 Substitution on Aminophenol	186
	4.2.5.2 Alternative Ketene Generators	192
4.2.6	Extension to Benzoquinolizinones	204
4.2.7	Reactions of 8-Hydroxyquinolizinones	210
4.2.8	Reactions at 8-Hydroxy Group	211
	4.2.8.1 Alkylations of 8-Hydroxyquinolizinones	211
	4.2.8.2 Acetylations of 8-Hydroxyquinolizinones	212
4.2.9	Electrophilic Substitution Reactions	218
	4.2.9.1 Reaction with Trifluoroacetic Acid	219
	4.2.9.2 Reaction with Diazonium Salts	224
	4.2.9.3 Halogenation of 8-Hydroxyquinolizinones	229
	4.2.9.4 Formylation of 8-Hydroxyquinolizinones	234
	4.2.9.5 Nitration of 8-Hydroxyquinolizinones	237
	4.2.9.6 Overview of Electrophilic Substitution Reactions	238
4.2.10	Hydrogenation of 8-Hydroxyquinolizinones	239
4.3	Conclusion	247
4.4	Experimental	248

Chapter 5 – Synthesis of Pyrido[2,3-*d*]pyridazinediones by FVP

5.1	Introduction	289
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5.2	Discussion	291
5.2.1	Pyrolysis of compounds 5.1 – 5.3	291
5.2.2	Pyrolysis of compounds 5.7 – 5.8	294
5.3	Conclusion	302
5.4	Experimental	303
Chapter 6 – Synthesis of <i>N</i>-Unsubstituted 3-Hydroxypyrroles and 1<i>H</i>-Pyrrol-3(2<i>H</i>)-ones by FVP		
6.1	Introduction	307
6.2	Discussion	314
6.2.1	Introduction	314
6.2.2	Further Examples	319
6.2.3	Non-ester Based Cyclisations	320
6.2.4	Tautomerism of Hydroxypyrroles	323
6.2.5	Alternative Ketene Generators	325
6.2.6	Synthesis of 3-Hydroxypyrrole by FVP	327
6.2.7	Tautomerism of 3-Hydroxypyrrole	329
6.2.8	Reactions of 3-Hydroxypyrrole	332
	6.2.8.1 Protonation in TFA/ <i>d</i> -TFA	333
	6.2.8.2 Reaction with Diazonium Salts	335
	6.2.8.3 Reaction with Dimethyl acetylenedicarboxylate	337
	6.2.8.4 Reaction with Methoxymethylene Meldrum's Acid	339
	6.2.8.5 Acetylation of 3-Hydroxypyrrole	341
6.3	Conclusion	343
6.4	Experimental	345
References		356
Appendix 1: Crystallography data for compound 4.127		364
Appendix 2: Crystallography data for compound 4.179		371
Appendix 3: Computational data for Energy surface in figure 4.9		378

Abbreviations

δ_H, δ_C	chemical Shift
DMSO	dimethyl sulfoxide
DCM	dichloromethane
THF	tetrahydrofuran
DMF	<i>N,N</i> -dimethylformamide
MgSO ₄	anhydrous magnesium sulfate
NaHCO ₃	sodium hydrogen carbonate
PPh ₃	triphenylphosphine
Pd/C	palladium on carbon
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine) palladium (0)
mol	moles
NMR	nuclear magnetic resonance
s	singlet
d	doublet
t	triplet
m	multiplet
br	broad
<i>J</i>	coupling constant
quat	quaternary carbon
MHz	megahertz
°C	degrees Celsius
mp	melting point
bp	boiling point
lit.	literature
<i>m/z</i>	molecular ion mass
EI	electron impact ionisation
ESI	electrospray Ionisation
h	hours
min	minutes
cm ³	cubic centimetres
g	grams

conc.	concentrated
aq.	aqueous
sat.	saturated
w	weight
T_f	furnace temperature
T_i	inlet temperature
P	pressure
t	time
B3LYP	Becke 3-parameter, Lee Yang Parr
HF	Hartrees
MP2	Møller-Plesset
DFT	density functional theory
HFIP	hexafluoroisopropanol
NBS	<i>N</i> -bromosuccinimide
DBDMH	<i>N,N'</i> -dibromo-5,5-dimethylhydantoin
DMAP	<i>N,N</i> -dimethylaminopyridine
HMDS	1,1,1,3,3,3-hexamethyldisilazane

Chapter 1

The Effect of Scale on Conversion in Flash Vacuum Pyrolysis Experiments

1.1 Introduction

Flash Vacuum Pyrolysis (FVP) is a gas phase technique, in which a substrate is placed in a pyrex tube and heated using a Kugelrohr oven under vacuum. The substrate sublimates and passes through a silica tube, heated in a furnace. Once in the hot zone of the furnace, bond breaking and making processes can occur to give a product. The product(s) from this reaction are then trapped in a U-shaped trap cooled in liquid nitrogen. The apparatus is illustrated in figure 1.1.

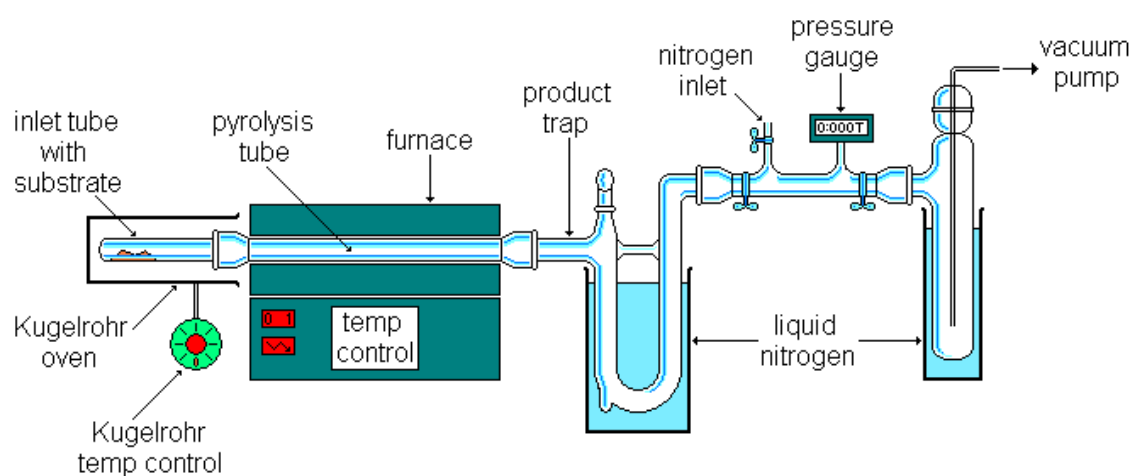
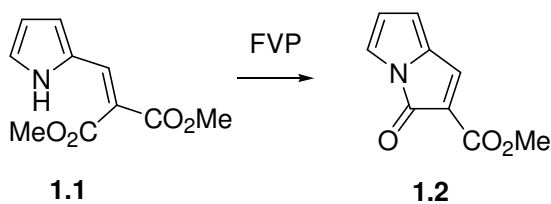


Figure 1.1 Flash Vacuum Pyrolysis apparatus

FVP is suited towards high energy intermediates, such as radicals or ketenes, and generally intramolecular reactions are favoured, though some intermolecular reactions, such as the coupling of benzyl radicals,¹ are possible.

A previous study¹ has focussed on the controllable variables in a FVP experiment: Furnace temperature, pressure variation, throughput rate, furnace packing materials and 'catalysts'. The model system studied was the conversion of the pyrrole methyldene malonate **1.1** to the pyrrolizinone **1.2** (Scheme 1.1).



Scheme 1.1 Pyrolysis of compound **1.1**

The furnace temperature would be considered the most important parameter in an FVP experiment. Typically temperature-conversion plots are integral to optimising FVP experiments. These plots are typically a sigmoidal shape, due to the Boltzmann distribution of energy in the system. The reaction of **1.1** to **1.2** occurs within a 150 °C region, beginning at 350 °C with full conversion to **1.2** occurring at 650 °C.

Pressure was also shown to be an important variable, due to the increased contact time of the molecules in the furnace. Increasing the pressure was demonstrated by the pyrolysis of **1.1** at 500 °C. At standard FVP conditions (10^{-2} Torr) the conversion was 45%, increasing the pressure by an order of magnitude (10^{-1} Torr) increases the conversion to 90%, which becomes almost quantitative at 1 Torr.

Throughput rate was shown to be unimportant in this example, with no observable effect on the conversion of the model system.

Furnace packing materials were shown to have dramatic effects on FVP experiments. The temperature required for complete conversion of **1.1** to **1.2** is lower with a packing of silica tubes and the temperature reaction range, over which the conversion occurs becomes narrower than without the packing. The position of the packing is also important with the optimal position being towards the trap end of the furnace tube. The implication of this result is that the packing material causes the molecules to experience a longer contact time in the hot zone of the furnace tube (due to a slower flow rate).

1.2 Discussion

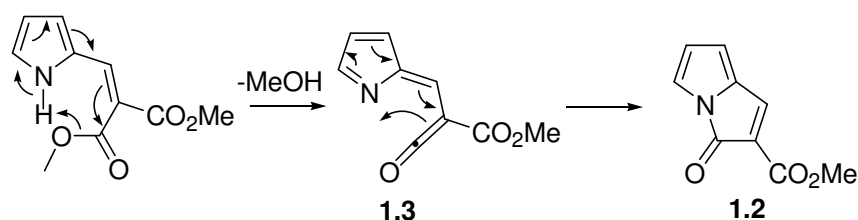
Typically, there are two types of FVP experiments that are carried out: matrix isolation and synthetic experiments. Matrix isolation experiments involve the

trapping of the intermediates in an argon matrix at low temperature (*ca.* 10 K), where they can be studied by spectroscopic methods, such as IR spectroscopy.² This is highly useful in studying the mechanism of a reaction

Typical synthetic FVP experiments are performed on a scale of 0.5 g, due to the ease of purification by chromatography on this scale.³ It is known that it is possible to pyrolyse upto 100 g of a precursor, as performed by Durham Organics.⁴ This is an isolated example however. To be useful as a synthetic methodology, an understanding of any inherent factors, which might complicate the use of FVP in general on a multigram scale, is needed.

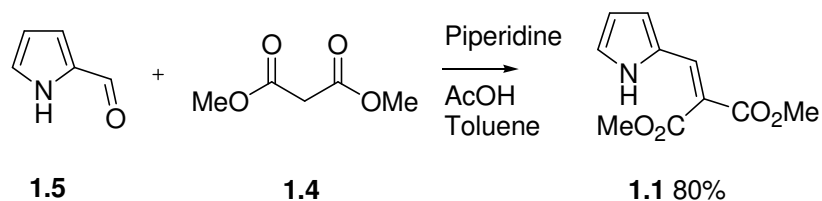
1.2.1 Model Reaction 1: Pyrrolizinone Formation

As previously mentioned, the work¹ in this area has been focussed on using the pyrolysis of pyrrole methyldene malonate **1.1** to give the pyrrolizin-3-one **1.2** (Scheme 1.1). Upon pyrolysis, the compound undergoes loss of methanol to generate ketene **1.3**, which can then undergo electrocyclicisation to give the pyrrolizinone **1.2** (Scheme 1.2).



Scheme 1.2 Mechanism for the formation of compound **1.2**

For ease of comparison, this reaction was chosen as the starting point for this study into the effects of scale on the pyrolysis. The precursor **1.1** was made using a Knoevenagel condensation of dimethyl malonate **1.4** with pyrrole-2-carboxaldehyde **1.5** in 80% yield after distillation (Scheme 1.3)



Scheme 1.3 Synthesis of compound **1.1**

The temperature profile for the reaction has already been reported¹ and from it 550 °C was chosen as initial temperature to start the study. The scale-conversion plot at 550 °C is shown below (Figure 1.2)

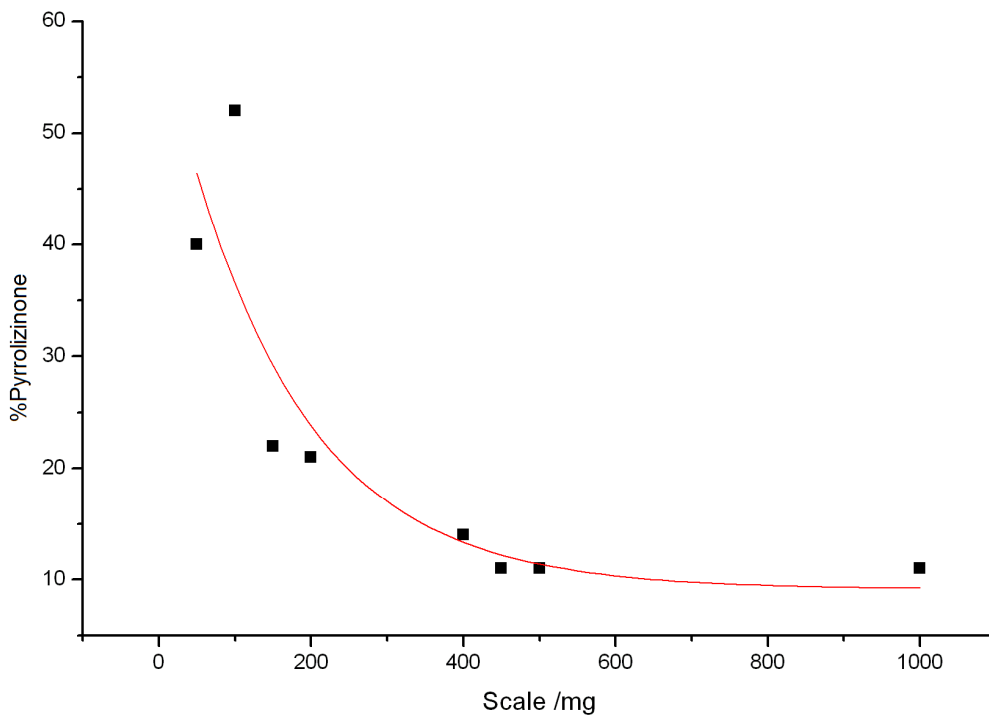


Figure 1.2 Scale-Conversion plot for the pyrolysis of compound **1.1** at 550 °C

Surprisingly, the conversion to **1.2** proved to be significantly scale-dependent. From figure 1.2, the large changes in conversion (around 30 – 40%) occur in the region from 50 mg to 400 mg. At larger scales, the change in conversion is small (ca. 5%) and within experimental error.

Since at scales approaching 1 gram, the conversion drops to around 10%, the furnace temperature was increased to 600 °C, in order to see if this effect was a general trend and if this trend continued past 1 gram. The scale-conversion plot is shown below (Figure 1.3)

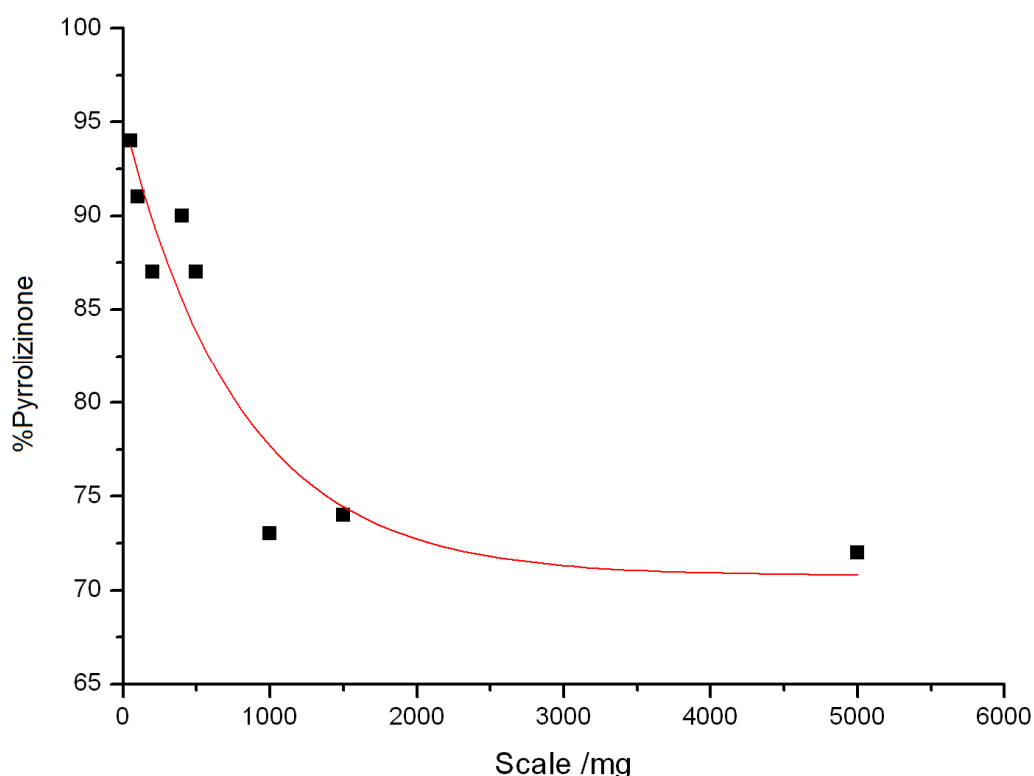


Figure 1.3 Scale-Conversion plot for the pyrolysis of **1.1** at 600 °C

At 600 °C, a similar pattern is observed as at 550 °C. The large changes in conversion are observed at the smaller scales (around 50 mg to 500 mg) and smaller changes are observed at the larger scales. An important factor in FVP experiments is the contact time. The contact time (CT) may be calculated from the following equation (Equation **1.1**).⁵

$$CT = 273/T \times V/22.4 \times P/760 \times t/m$$

Equation 1.1 Equation for calculating contact time, where T is the temperature, V is the volume of the hotzone, P is the pressure of the system, t is the time of the pyrolysis and m is the number of moles pyrolysed.

From equation **1.1**, T, V and P are all constants, which makes the contact time proportional to the last portion of the equation. This is the inverse of the throughput rate, so a plot of scale against the throughput rate should show a relationship if the scale is affecting the contact time. These plots are shown below (Figure **1.4**)

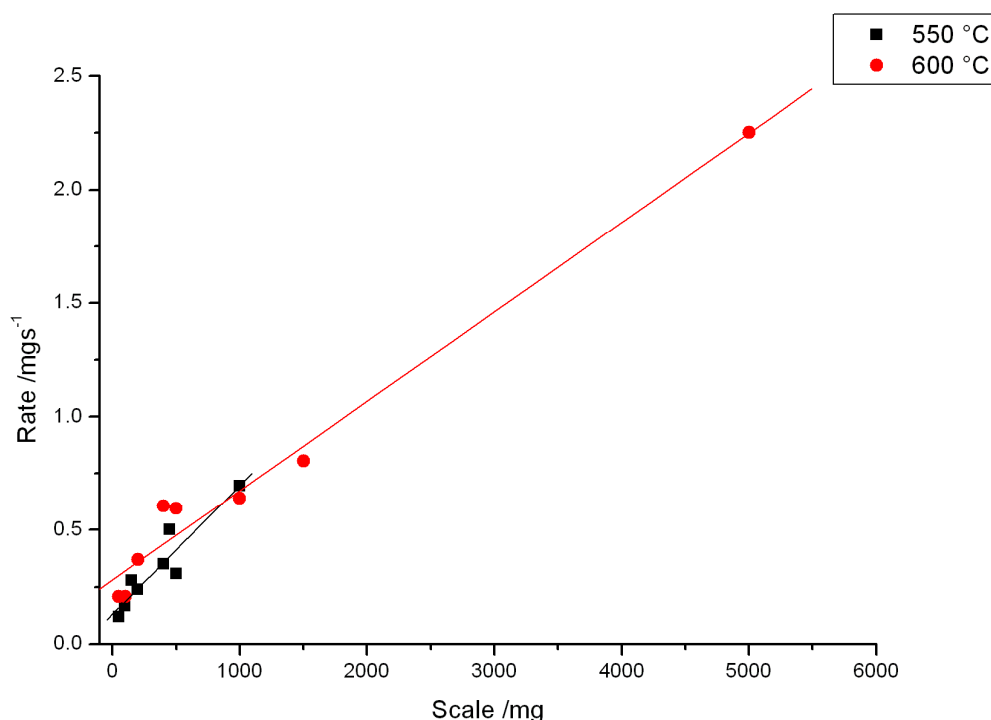


Figure 1.4 Plot of scale against throughput rate

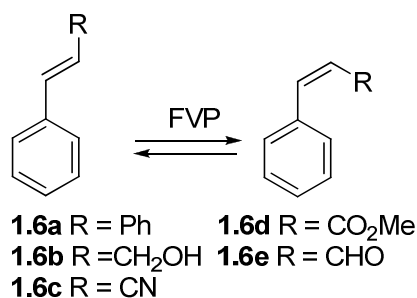
From figure 1.4, we can see that as the scale increases the throughput rate also increases at both pyrolysis temperatures. Since the contact time is proportional to the inverse of the throughput rate, the contact time is decreasing with the increase in scale. This is shown in the conversion, which decreases as the scale increases.

Other systems were investigated in order to discover whether this was a general trend for all FVP experiments. This was due to two reasons: (1) the starting material **1.1** was not available in larger quantities and (2) an intramolecular rearrangement would be easier to study, due to the lack of any side products.

1.2.2 Model Reaction 2: *E/Z* Double Bond Isomerisation

Under thermal conditions, it is well known that alkenes can undergo *E-Z* isomerisation, although the temperatures required to do so are high. Under FVP conditions, it is known that *trans* isomers of pyrolysis precursors react to give the

cyclised products, which can only form from the *cis* isomer.⁶ Indeed it has been shown that isomerisation of alkenes such as **1.6a-e** can occur under FVP conditions⁶(Scheme 1.4).



Scheme 1.4 Isomerisation of compound **1.6a-e**

In these compounds, the extent of the isomerisation was found to be dependent on the R group, giving the temperature profiles seen in figure 1.5 (below)

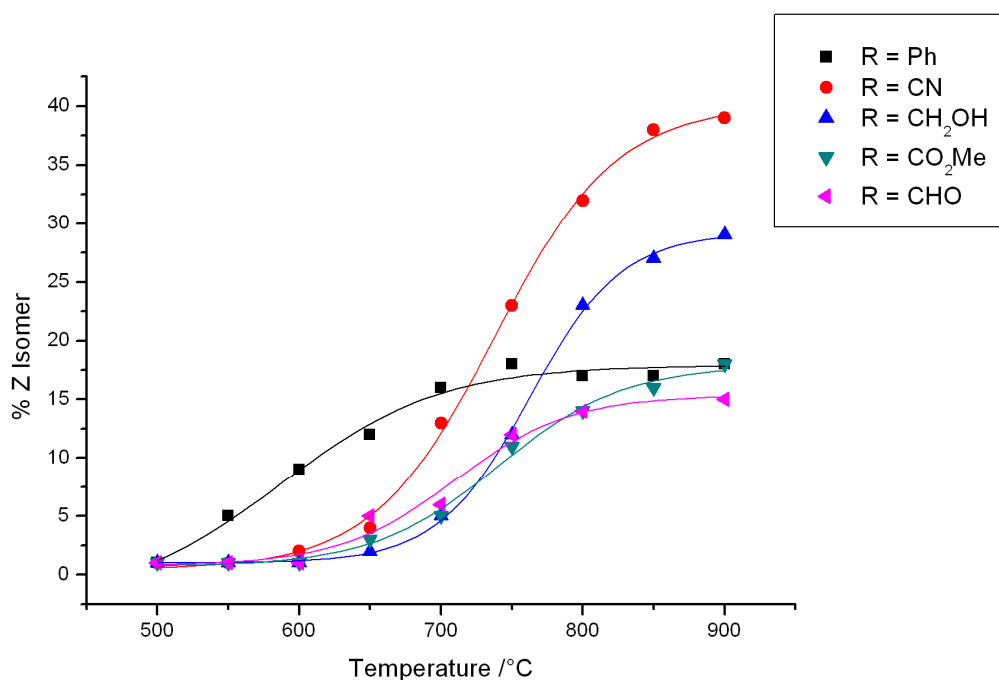


Figure 1.5 Temperature profile for compound **1.6a-e**

From figure 1.5 it can be seen that the highest amount of isomerisation occurs when the R group is a nitrile (compound **1.6c**). Using these data, cinnamonnitrile **1.6c** was chosen as the model system, due to the high amount of isomerisation observed under FVP conditions. It is commercially available as the *trans* isomer in 97% purity.

Based on the previous work, scaling the reaction below 0.5 gram was not carried out, as the region of interest is in the multigram region. The pyrolysis temperature, based on the temperature profile in figure 1.5, was chosen to be 750 °C. Keeping the other conditions constant, the following graph of scale against conversion was obtained (Figure 1.6)

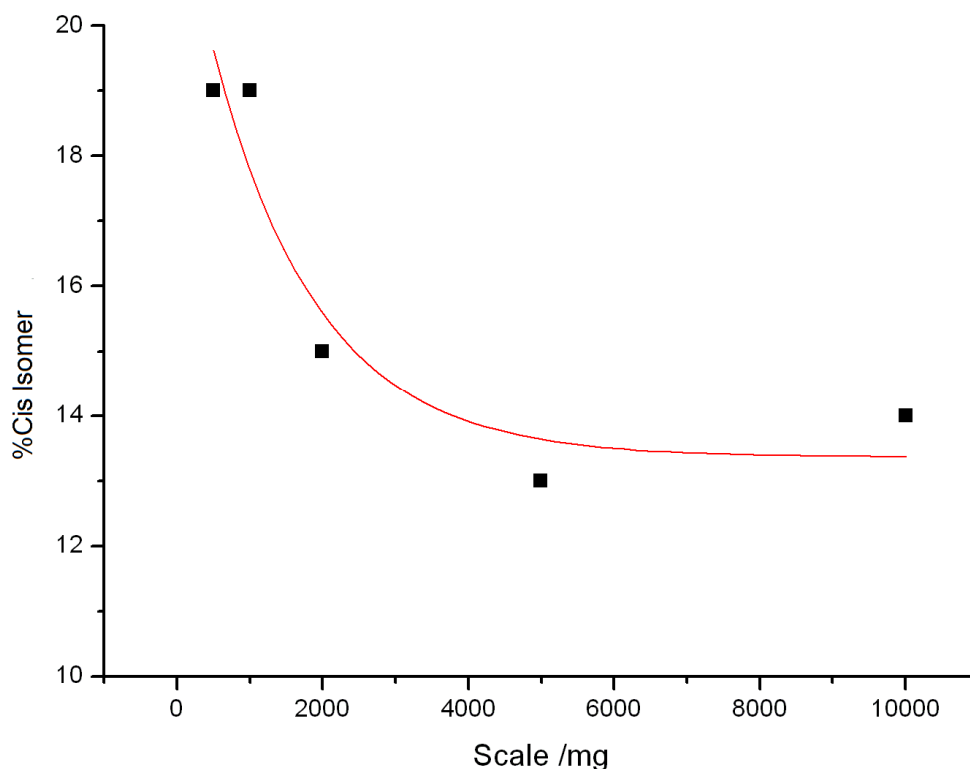


Figure 1.6 Scale-Conversion plot for the pyrolysis of compound **1.6c**

From figure 1.6, the scale can be seen to have a small effect (*ca.* 5%) on the conversion. On scales > 2 grams, the conversion is essentially flat, with only small changes within experimental error.

As previously mentioned, the contact time is affected by a number of factors. The volume of the hot zone was one of these factors in the equation to calculate the contact time and is directly proportional to the contact time. From this, a larger volume in the hot zone should lead to an increase in the conversion, while a smaller volume should lead to a decreased conversion.

The wide and narrow furnace tubes were designed around internal diameters of *ca.* 35 and 15 mm, in comparison with the standard tube diameter of *ca.* 25 mm. The three furnace tubes are shown in figure 1.7 for comparison purposes.

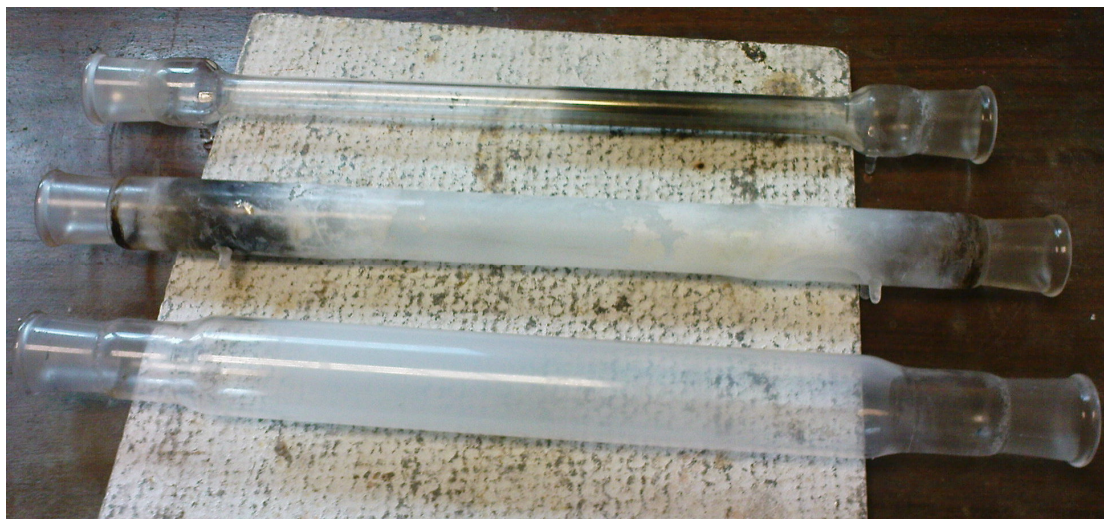


Figure 1.7 Photograph of the narrow (top), normal (middle) and wide (bottom) furnace tubes

Figure 1.8 (below) shows the scale-conversion plot for the isomerisation of cinnamonnitrile **1.6c** in all three furnace tubes.

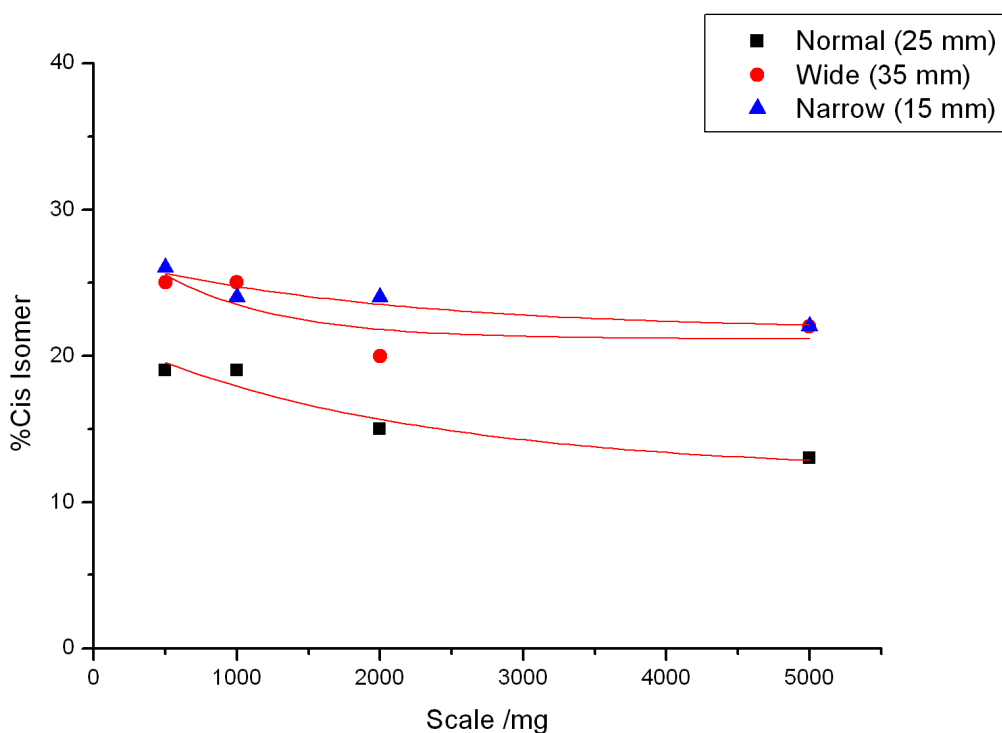


Figure 1.8 Scale-conversion plot for the pyrolysis of compound **1.6c** for all three furnace tubes

From figure **1.8**, the conversions can be seen to be independent of scale past 0.5 g, with only small changes occurring, with all three furnace tubes. Both furnace tubes show an increase in conversion of *ca.* 5 – 10% over the normal diameter furnace tube. As with the pyrrolizinone model system, these changes in conversion might be due to a decrease in the contact time, which can be shown by means of throughput rate-scale plot (Figure **1.9**)

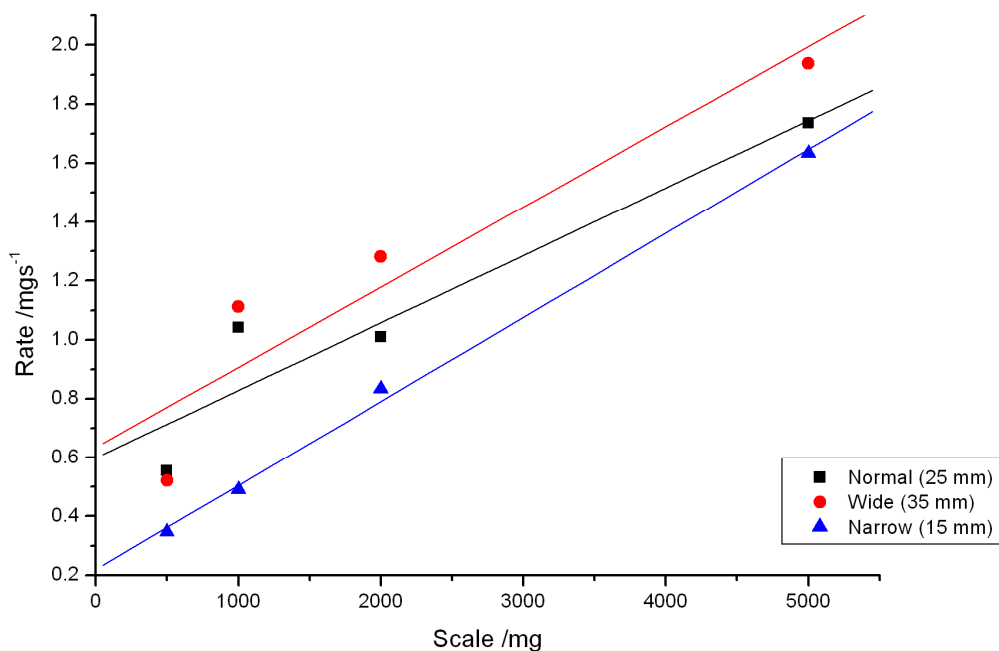


Figure 1.9 Plot of rate against scale for the pyrolysis of compound **1.6c**

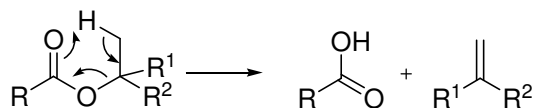
From figure **1.9**, it can be seen that the throughput rate is increasing with scale, as was the case with the pyrrolizine model system. This is true across all three furnace tubes.

The result from the wider furnace tube was expected, but the narrower furnace tube was not as expected. This may be explained by an increased number of collisions in the hot zone of the furnace tube, which has a similar effect to increasing the pressure in the system. From the equation to calculate the contact time (figure **1.10**), the pressure is directly proportional to the contact time, so an increase in the pressure leads to an increase in the conversion of the reaction

.

1.2.3 Model Reaction 3: De-Esterification of Alkyl Benzoates

A well known reaction of alkyl esters higher than methyl under FVP conditions is the elimination of the alkyl group as an alkene, by a retro-ene mechanism, to give the free acid.⁷ The mechanism is shown below (Scheme **1.5**)



Scheme 1.5 De-esterification of an alkyl ester

The main difference between this model system and the isomerisation reaction discussed previously is that in this reaction, two moles of product are produced per mole of reactant.

Two model systems were chosen for this reaction: ethyl benzoate **1.7** and *tert*-butyl benzoate **1.8**. The difference between the two systems is the temperature required to cause the loss of the ester, which is lower for the *tert*-butyl ester than the ethyl ester. In both examples the product is benzoic acid **1.9** and is easily identified from its ^1H NMR spectrum.

Figure **1.10** shows the effect on scale on the pyrolysis of ethyl benzoate **1.7** for normal, wide and narrow furnace tubes.

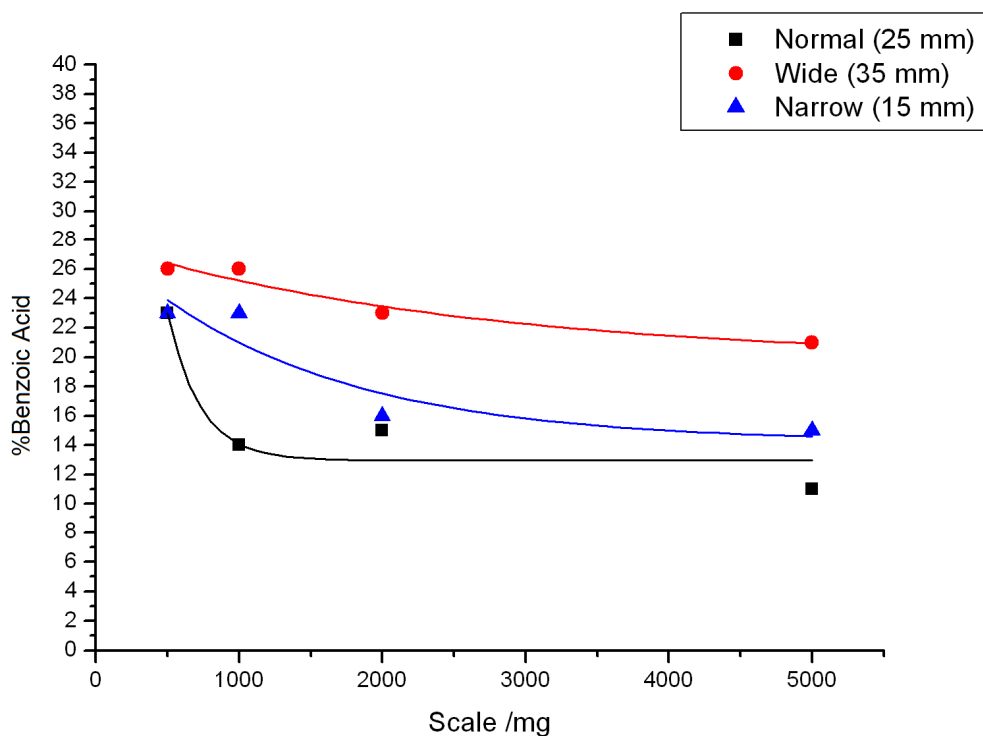


Figure 1.10 Scale-Conversion plot for the pyrolysis of compound **1.7**

Figure 1.11 shows the effect on scale on the pyrolysis of *tert*-butyl benzoate **1.8** for normal, wide and narrow furnace tubes.

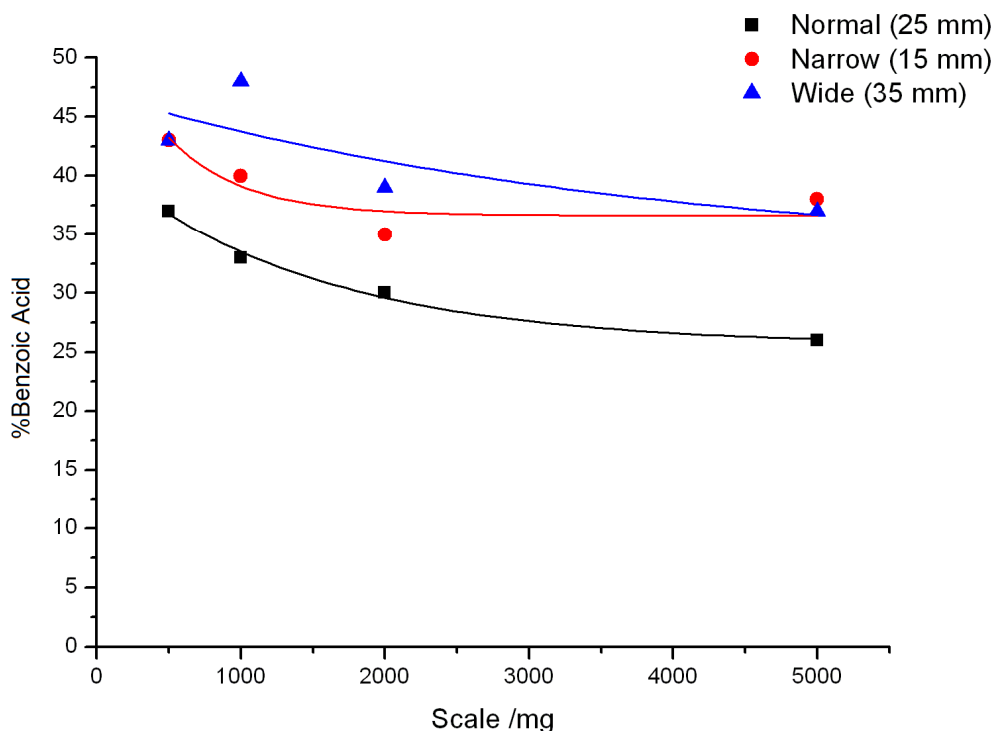


Figure 1.11 Scale-Conversion plot for the pyrolysis of compound **1.8**

With both the benzoate systems, an initial decrease is observed with the ‘normal’ furnace tube between 0.5 and 1 g of around 5 – 10% followed by the conversion levelling off. The other furnace tubes again show higher levels of conversion, generally around 10%, over the ‘normal’ furnace tube. Throughput rate-scale plots are shown in Figures 1.12 and 1.13 (below)

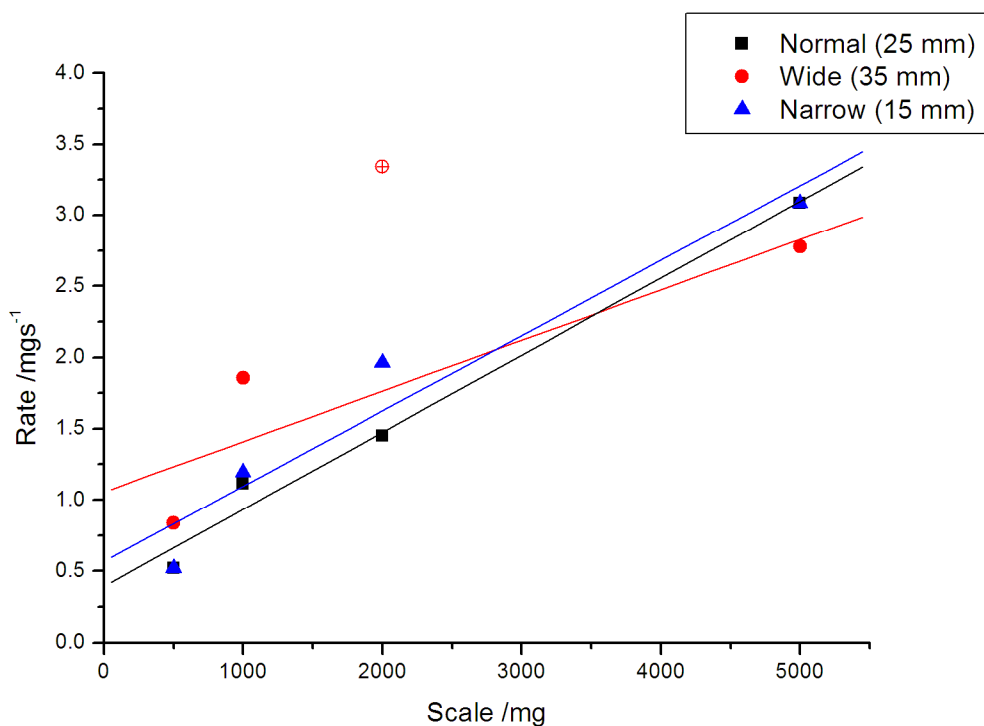


Figure 1.12 Plot of rate against scale for the pyrolysis of compound **1.7** (Point at for wide furnace tube at 2000 mg was ignored for the best fit straight line)

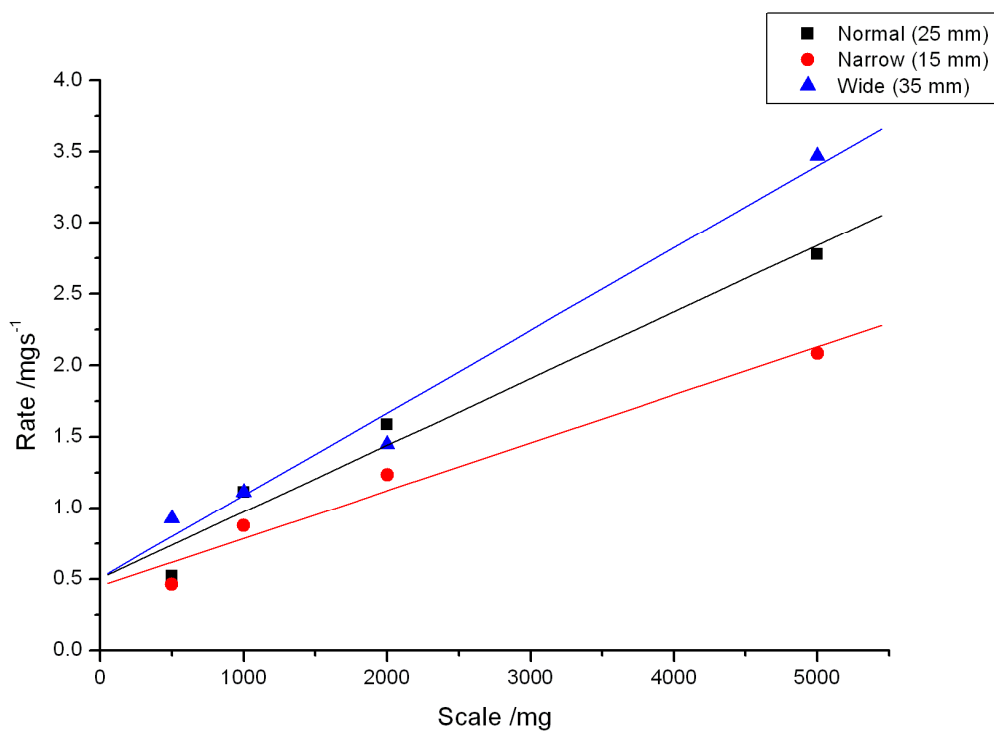


Figure 1.13 Plot of rate against scale for the pyrolysis of compound **1.8**

From figures **1.12** and **1.13**, the general trend is same as for the previous two systems: as the scale increases, the throughput rate increases, which would lead to a decreased contact time in the hot zone of the furnace tube.

1.2.4 Overview

For all four model reactions, a general trend is observed with regards to scale. Based on the results obtained scale does not appear to affect conversion on larger scales (>0.5 g), which are desired for preparative pyrolyses. From the pyrrolizinone model, the big changes (of around 20%) in conversion with scale occur between 50 mg and 500 mg. All four systems show small changes of around 5%, generally within experimental error, at scales of 0.5 g or larger.

The contact time is one of the more important factors in FVP experiments. As the scale increases, the throughput rate, which is inversely proportional to the contact time, was found to increase. This meant that the contact time was decreasing with scale, leading to the observed decrease in conversion. This was shown to be the case from the plots of scale against throughput rate.

The effect of furnace tube diameter was found to effect the conversion of the model reactions. Both wide and narrow furnace tubes had the effect of increasing the conversion to product, with typical increases of around 10%. The wide furnace tube, is due to an increase in the contact time, which is directly proportional to the volume of the hot zone of the furnace tube. The narrow furnace tube might be explained by an increase in the number of collisions that occur in the hot zone of the furnace tube. The increased number of collisions leads to an increase in the effective pressure in the system, which as observed in the previous study,¹ leads to an increase in the conversion observed.

1.3 Conclusion

From the pyrrolizinone system, the big changes in conversion are observed in the lower scales, between 50 and 500 mg. With scales above 500 mg, the changes are small in the region of 5 – 10% at most, in comparison to the 30 – 40 % changes

observed in the 50 – 500 mg scale region. These changes are observed across all four model systems, with all types of furnace tubes. The effect of the diameter of the furnace tubes was also investigated and both wide and narrow diameter furnace tubes were found to be marginally beneficial in the percentage conversion observed. From this work, it has been shown that there is no inherent reason that scale-up of FVP experiments should not be successful.

Experimental

Instrumentation

Nuclear Magnetic Resonance (NMR) Spectroscopy

¹H and ¹³C NMR spectra were recorded using Varian Gemini 200 (200 MHz), Bruker AC250 (250/63 MHz), WH360 (360/90 MHz) and AVA500 (500/125 MHz) spectrometers, for solutions in deuteriochloroform unless otherwise stated. ¹⁹F NMR spectra were recorded using the Bruker AC250 (235 MHz) spectrometer. The spectra obtained from AC250 were recorded by Mr J. R. A. Millar, Mr. J. Bella and Dr. M. Cremoux. All other spectrometers were operated by the author with some assistance from Mr. J. R. A. Millar, Mr. J. Bella and Dr. D. Reed.

Chemical shifts are quoted in parts per million (ppm) relative to tetramethylsilane (δ =0.0) and coupling constants (J) are given in Hz. ¹³C signals represent CH resonances unless otherwise stated.

Mass Spectroscopy

Low resolution EI and high resolution EI/ESI were performed on a Thermomat 900XP spectrometer. Low resolution ESI spectra were performed on a Finnegan LCQ. Both spectrometers were operated by Mr. A. T. Taylor and all spectra are assumed to be EI, unless otherwise stated. GC-MS spectra were obtained on a VG Trio 1000 spectrometer, operated by the author and Dr. K. A. Johnston.

Elemental Analysis

Elemental analyses were performed by Ms. Sylvia Wilson at the University of St. Andrews Elemental Analysis Service.

Chromatography

Thin-layer chromatography was carried out on pre-coated aluminium sheets (0.2 mm, silica gel, Merck, grade 60) impregnated with an ultra-violet indicator. Dry flash chromatography was carried out on silica gel (Merck, grade 60, 230-400 Mesh, 60 Å) or alumina gel (basic Brockman 1, standard grade, ~150 Mesh, 58 Å). Crude material

was pre-adsorbed onto silica or alumina gel and then loaded onto the column. Solvent systems are specified for each reaction system.

Melting Points

Melting points were recorded using Gallenkamp melting point apparatus. Samples of compounds were recrystallised from appropriate solvents as necessary.

X-Ray Diffraction

Crystal structures were obtained and solved by Prof. S. Parsons, Mr. R. D. L. Johnstone and Ms. A. Collins on Bruker Smart APEX CCD with a graphite monochromator.

Commercial Chemicals

All commercial starting materials were obtained from Sigma Aldrich, Acros or Lancaster. Trifluoromethanesulfonic anhydride was obtained from Fluorochem. Palladium catalysts were obtained from Strem. Sodium hydride was washed with hexane and dried under high vacuum for 30 min prior to use.

Solvents

Solvents were generally obtained from Aldrich, Fisher or Rathburn, and were used without further purification.

Computational Studies

Computational studies were performed using the Gaussian03 program from Gaussian Inc., on the 'Hare' cluster managed by Dr. A. Turner and Dr. P. Richardson of the EaStCHEM research computing facility. Inputs were created using Planaria software's ArgusLab program and modified as necessary. DFT calculations were typically performed at B3LYP/6-31G** level and *ab initio* calculations to MP2/6-31G** level. Energies are quoted in Hartrees (HF). Transition states are optimised to a first order state (one negative frequency). All the data obtained from the calculations is contained on a DVD attached to this thesis in both .log and .doc formats.

Flash Vacuum Pyrolysis (FVP) Experiments

The apparatus used for FVP experiments is illustrated in Figure 1.14, based on a design by W. D. Crow of the Australian National University.

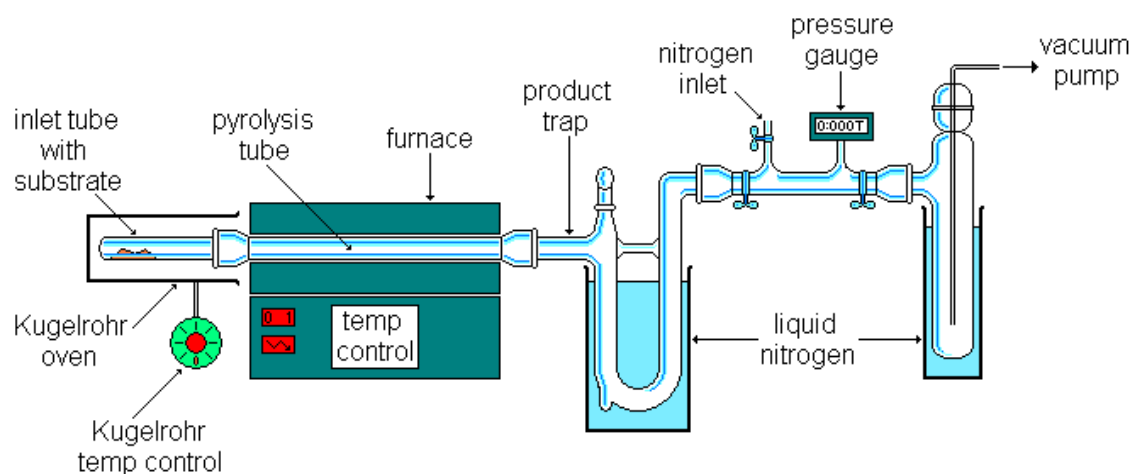


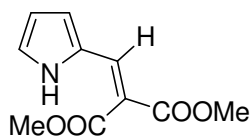
Figure 1.14 FVP apparatus

The system is evacuated by use of an Edwards Model ED100 high capacity oil pump to maintain the pressure in the region of $2.0 - 3.0 \times 10^{-2}$ Torr. A glass Kugelrohr oven is used to heat to the inlet tube in which the substrate is placed until it volatilises. The gaseous substrate passes through a silica tube ($30 \times 2.5 \text{ cm}^3$) heated by a Carbolite electronically controlled laboratory tube furnace (model number MTF 12/38/250). The products are captured at the end of the furnace in a U-shaped trap cooled in liquid nitrogen. Upon completion of the reaction, the pump is isolated and the trap allowed to warm to room temperature under a dry nitrogen atmosphere.

Small scale pyrolyses are generally performed using 20 – 50 mg of substrate. The entire pyrolysate is dissolved in a deuteriated solvent for examination by NMR spectroscopy of the crude reaction products. Preparative pyrolyses are performed using 0.1 g or more of substrate. The pyrolysate is removed from the U-tube by addition of a solvent (such as acetone or methanol), the solution is pipetted out of the trap and the solvent removed to give product.

Experimental Data For Chapter 1

Dimethyl 2-[(pyrrol-2-yl)methylidene]malonate⁸ **1.1**



Dimethyl malonate (6.60 g, 50.0 mmol), glacial acetic acid (20 drops) and piperidine (20 drops) were added to a solution of pyrrole-2-carboxaldehyde (4.75 g, 50.0 mmol) in the minimal amount of toluene and allowed to stir overnight. The solvent was removed and the product purified by bulb-to-bulb (Kugelrohr) distillation to give the product as a red-orange oil (8.37 g, 80%); δ_H 11.49 (1H, s, br), 7.73 (1H, s), 7.12 (1H, m), 6.73 (1H, m), 6.32 (1H, m), 3.85 (3H, s) and 3.82 (3H, s); δ_C 168.84 (quat), 167.41 (quat), 138.62, 127.52 (quat), 126.73, 124.70, 112.62 (quat), 111.92, 52.82 (CH₃) and 52.65 (CH₃).

FVP Experiments

The crude pyrolysates were treated differently depending on scale. On small scales (50 – 100 mg), the entire pyrolysate was dissolved in deuteriochloroform and the ¹H NMR spectrum recorded. For larger scales, the pyrolysate was dissolved in a quantity of DCM to give a set concentration and an aliquot of the solution taken. The DCM was removed, the sample dissolved in deuteriochloroform and the ¹H NMR spectrum recorded. The time for the pyrolysis is recorded from the appearance of product to the end of the pyrolysis.

Pyrolysis of Dimethyl 2-[(pyrrol-2-yl)methylidene]malonate **1.1**

The inlet temperature was set at 110 °C for these reactions. The product ratio was determined by ¹H NMR spectroscopy where the product **1.2** was characterised by the signal at $\delta_H = 7.8$ ppm and the precursor by the signal at $\delta_H = 7.6$ ppm.³

550 °C Pyrolyses

weight /mg	$P / \times 10^{-2}$ Torr	t /min	Compound 1.2 /%	Compound 1.1 /%
50	2.3 – 2.7	7	40	60
100	4.6 – 4.8	10	52	48
150	2.7 – 3.2	9	22	78
200	2.7 – 3.6	14	21	79
400	2.6 – 3.4	19	14	86
450	2.6 – 3.0	15	11	89
500	2.8 – 3.4	27	11	89
1000	2.3 – 2.9	24	11	89

600 °C Pyrolyses

weight /mg	$P / \times 10^{-2}$ Torr	t /min	Compound 1.2 /%	Compound 1.1 /%
50	2.9 – 3.4	4	94	6
100	2.7 – 3.0	8	91	9
200	2.6 – 3.2	9	87	13
400	2.6 – 2.8	11	90	10
500	2.8 – 2.9	14	87	13
1000	2.4 – 2.8	26	73	27
1500	2.5 – 3.2	31	74	26
2000	2.8 – 3.2	23	54	46
5000	1.4 – 2.2	37	72	28

Pyrolysis of *trans*-Cinnamionitrile 1.6c

The furnace temperature was set to 750 °C and the inlet temperature was set at 50 °C for these reactions. The product ratio was determined by ^1H NMR spectroscopy where the *trans*-isomer was characterised by the signal at $\delta_{\text{H}} = 5.77$ ppm and the *cis*-isomer by the signal at $\delta_{\text{H}} = 5.34$ ppm.⁹

25 mm Diameter Furnace Tube

Entry	Weight /mg	$P / \times 10^{-2}$ Torr	t /min	Ratio (cis:trans)
1	502.3	2.6 – 3.6	15	19:81
2	999.5	2.9 – 3.2	16	19:81
3	2000.2	2.2 – 2.9	33	15:85
4	4999.8	2.3 – 2.9	48	13:87
5	10006.1	3.0 – 3.6	56	14:86

35 mm Diameter Furnace Tube

Entry	Weight /mg	$P / \times 10^{-2}$ Torr	t /min	Ratio (cis:trans)
1	500.9	2.3 – 3.0	16	25:75
2	1006.1	2.7 – 3.2	15	25:77
3	2000.8	2.9 – 3.4	26	20:80
4	5001.0	2.9 – 3.0	43	21:79

15 mm Diameter Furnace Tube

Entry	Weight /mg	$P / \times 10^{-2}$ Torr	t /min	Ratio (cis:trans)
1	503.3	2.8 – 3.2	24	26:74
2	1002.7	2.5 – 2.6	34	24:76
3	2001.2	1.9 – 2.3	40	24:76
4	4999.4	1.1 – 1.9	51	22:78

Pyrolysis of Ethyl Benzoate 1.7

The furnace temperature was set to 700 °C and the inlet temperature was set at 40 °C for these reactions. The product ratio was determined by ^1H NMR spectroscopy where the product, benzoic acid **1.9**, was characterised by the signal at $\delta_{\text{H}} = 8.03$ ppm and the starting material by the signal at $\delta_{\text{H}} = 7.99$ ppm.

25 mm Diameter Furnace Tube

Entry	Weight /mg	$P / \times 10^{-2}$ Torr	t /min	Ratio (1.9:1.7)
1	500.8	2.6 – 3.0	16	23:77
2	1000.8	2.2 – 3.4	15	14:86
3	2000.5	2.2 – 2.8	23	15:85
4	5000.4	2.6 – 4.8	27	11:89

35 mm Diameter Furnace Tube

Entry	Weight /mg	$P / \times 10^{-2}$ Torr	t /min	Ratio (1.9:1.7)
1	500.7	2.6 – 2.9	10	26:74
2	1003.4	2.9 – 3.3	9	26:74
3	2005.4	2.2 – 2.9	10	23:77
4	5001.4	2.2 – 3.2	30	21:79

15 mm Diameter Furnace Tube

Entry	Weight /mg	$P / \times 10^{-2}$ Torr	t /min	Ratio (1.9:1.7)
1	500.8	2.7 – 3.0	16	23:77
2	1002.4	2.3 – 2.5	14	22:78
3	2000.1	2.3 – 2.8	17	16:84
4	5000.9	3.0 – 3.2	27	15:85

Pyrolysis of *tert*-Butyl Benzoate 1.8

The furnace temperature was set to 500 °C and the inlet temperature was set at 40 °C for these reactions. The product ratio was determined by ^1H NMR spectroscopy where the product, benzoic acid **1.9**, was characterised by the signal at $\delta_{\text{H}} = 8.05$ ppm and the starting material by the signal at $\delta_{\text{H}} = 7.99$ ppm.

25 mm Diameter Furnace Tube

Entry	Weight /mg	$P / \times 10^{-2}$ Torr	t /min	Ratio (1.9:1.8)
1	499.8	2.3 – 2.8	16	37:63
2	999.9	2.0 – 2.9	15	33:67
3	2000.5	2.3 – 3.2	21	30:70
4	5000.0	2.3	30	26:74

15 mm Diameter Furnace Tube

Entry	Weight /mg	$P / \times 10^{-2}$ Torr	t /min	Ratio (1.9:1.8)
1	501.5	2.4 – 3.6	18	43:57
2	1000.4	2.3 – 2.9	19	40:60
3	1999.9	2.3 – 3.2	27	35:65
4	5000.5	2.4 – 4.0	40	38:62

35 mm Diameter Furnace Tube

Entry	Weight /mg	$P / \times 10^{-2}$ Torr	t /min	Ratio (1.9:1.8)
1	499.8	2.6 – 3.6	9	43:57
2	1000.0	2.3 – 3.2	15	48:52
3	2001.2	2.3 – 3.6	23	39:61
4	5000.0	2.3 – 3.6	24	37:63

Chapter 2

Pyrolysis of *Ortho*-substituted Anilinomethylene Meldrum's Acid Derivatives

Introduction

The term “quinolinones” used in this thesis refers exclusively to *1H*-quinolin-4-ones. Quinolin-4-ones have generated much interest in the literature, due to their antibacterial properties.¹⁰ The first market quinolinone developed was Nalidixic acid, but since then over 10,000 molecules have been patented.¹⁰ The basic structure **2.1** is given in figure **2.1**, with the appropriate numbering scheme.

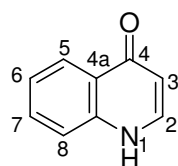
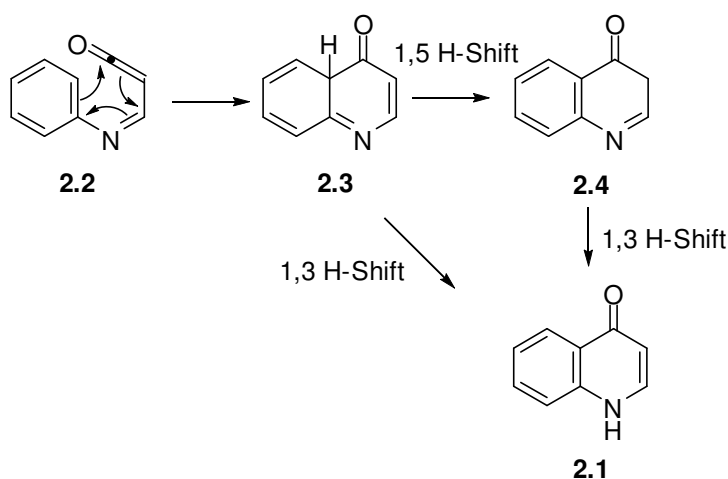


Figure 2.1 Structure of quinolin-4-one **2.1** with the numbering system

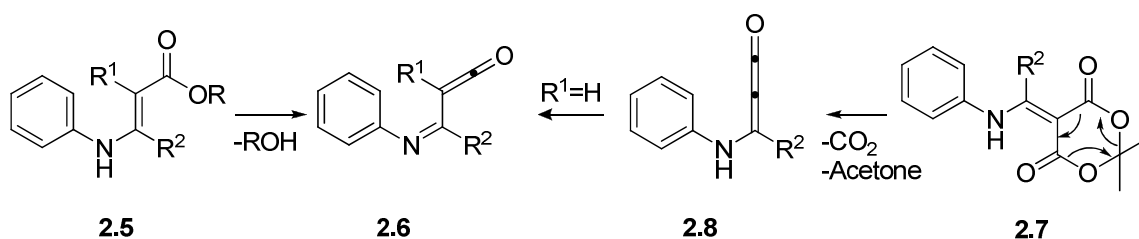
The typical bond-forming step for the synthesis of quinolinones **2.1** is between C4 and C4a¹¹ and is usually accomplished by the cyclisation reaction of an imidoylketene **2.2**. The mechanism for the cyclisation is given in scheme **2.1**.



Scheme 2.1 Mechanism for the formation of quinolinone **2.1**

Electrocyclisation of the imidoylketene **2.2** generates the intermediate **2.3**. This can undergo two pathways: a direct (formally disallowed in the intramolecular fashion) 1,3 hydrogen shift to give the quinolinone **2.1** or a 1,5 hydrogen shift to generate intermediate **2.4**, which can then undergo the 1,3 hydrogen shift to give the product.

The imidoylketene is usually generated by two methods: The first involves the thermolysis of acrylate esters **2.5**, which proceeds by loss of an alcohol to give the imidoylketene **2.6** (Scheme 2.2). This is commonly known as the Conrad-Limpach reaction and is typically performed in high boiling solvents, such as Dowtherm, although it can also be performed under acidic conditions using reagents such as polyphosphoric acid or phosphorus pentoxide.¹¹ The second method involves the pyrolysis of methylene Meldrum's acid derivatives **2.7**, which lose acetone and carbon dioxide to give the methyleneketene **2.8**. This undergoes a 1,3 hydrogen shift to give the imidoylketene **2.6** ($R^1 = H$), which is allowed in this case due to the in-plane orbitals on the ketene (Scheme 2.2).



Scheme 2.2 Generation of Imidoylketene **2.6** from precursors **2.5** and **2.7**

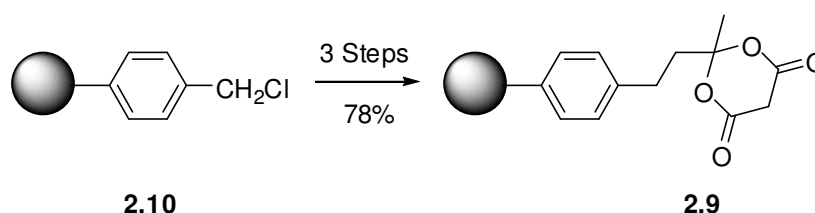
From the structure of imidoylketene **2.6**, it can be seen that substitution in the 2- and 3-positions of the quinolinone arises from the ketene portion of the molecule, while substitution in the aniline ring gives substitution in the 5, 6, 7, and 8-positions of the molecule. From the Meldrum's acid precursors, substitution in the 3-position is not possible, due to the initial 1,3 hydrogen shift of the methyleneketene needed to give the imidoylketene.

This review focuses on the synthesis of quinolinones from the Meldrum's acid derivatives, rather than the acrylate ester route. It will cover the synthetic methods used to obtain the quinolinones, modification of the Meldrum's acid moiety (leading to 2-substituted quinolinones), work on regioselectivity of the electrocyclisation and applications of these methods to the synthesis of unusual quinolinone derivatives.

The pyrolysis is typically performed in either the solution phase or the gas phase. The solution phase pyrolysis is a well known reaction, first reported in 1969.¹² Typically,

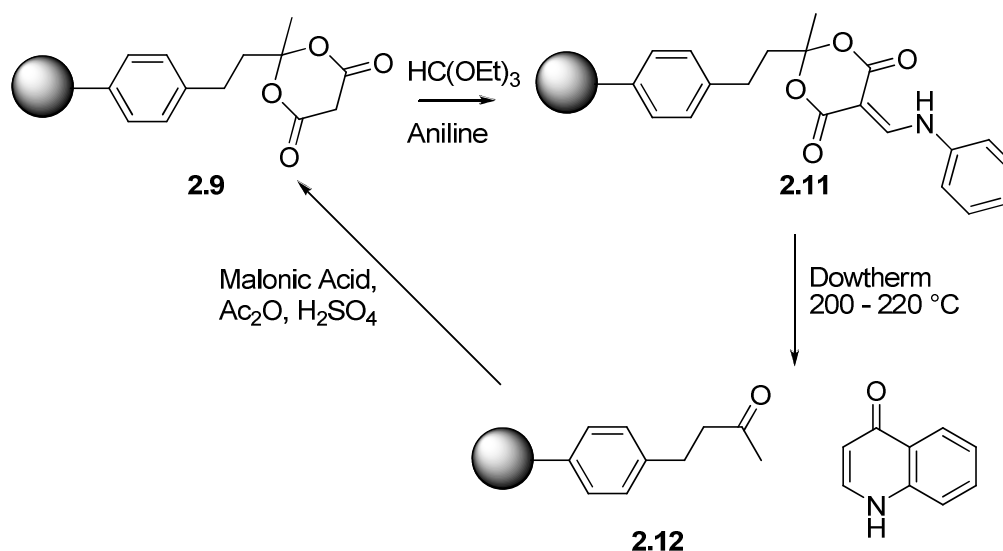
high boiling solvents, such as Dowtherm A, are used and the quinolinones are isolated by precipitation from the solution. The gas phase route involves flash vacuum pyrolysis (FVP) of the compound at furnace temperatures of around 600 °C at pressures of around 10^{-2} Torr.¹³

The formation of quinolinones has also performed using solid-phase methodology.¹⁴ This utilises a tethered Meldrum's acid **2.9**, which was synthesised from the Merrifield resin **2.10** in three steps (Scheme 2.3)



Scheme 2.3 Synthesis of resin bound Meldrum's acid **2.9**

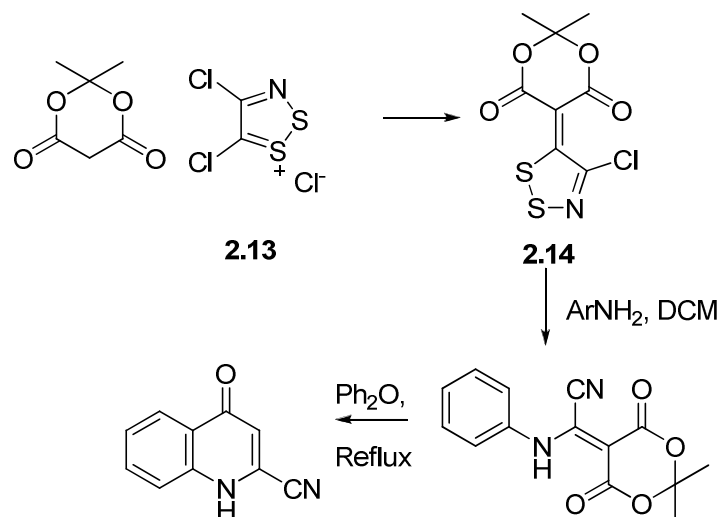
Reaction of resin bound Meldrum's acid **2.9** with triethyl orthoformate and the appropriately substituted aniline gave the pyrolysis precursor **2.11**. Heating **2.11** at 220 – 240 °C for 20 minutes gave the quinolinone and returned the resin **2.12**, which could be reconverted back into the Meldrum's acid resin (Scheme 2.4).



Scheme 2.4 Synthesis and pyrolysis of compound **2.11**

Nitrile groups can be introduced into the Meldrum's acid precursor by reaction of

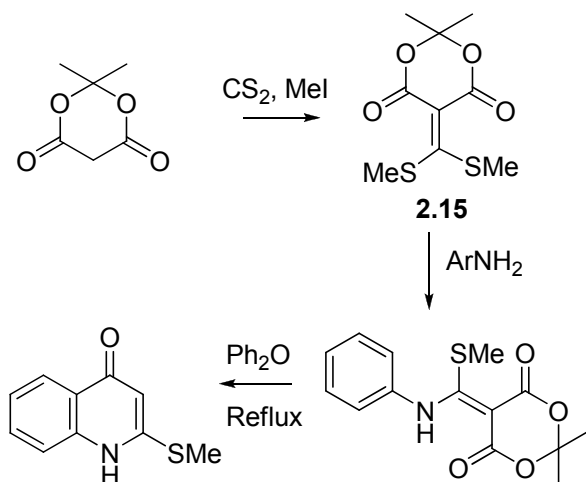
compound **2.14**, synthesised from Appel's salt **2.13** and Meldrum's acid, with the appropriate aniline in good yields (80-90%).¹⁵ Solution phase pyrolysis of the compound gave the 2-cyanoquinolinone in moderate to good yields (Scheme 2.5).



Scheme 2.5 Synthesis of 2-Cyanoquinolinones from Appel's salt **2.13**

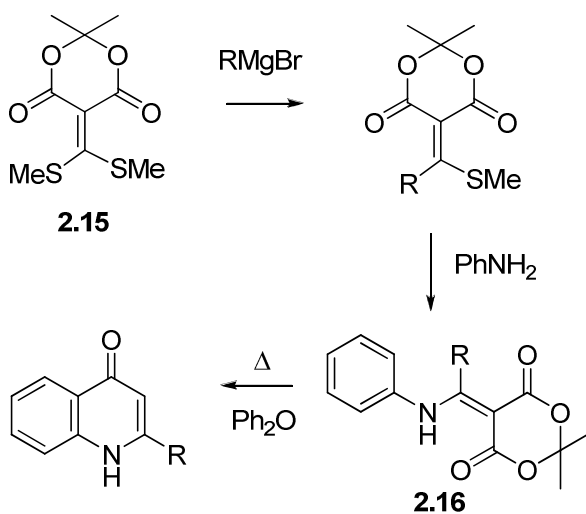
The main drawback of this reaction is the long reaction time (>20 hours) required to synthesis the pyrolysis precursors. However, this does offer a simple route to 2-cyanoquinolinones.

Thiomethyl groups can also be introduced into the 2-position of quinolinones.¹⁶ Reaction of Meldrum's acid with carbon disulfide and iodomethane gives the bis(thiomethyl)methylene Meldrum's acid **2.15**, which can be reacted selectively with one equivalent of the aniline to give the pyrolysis precursor. Solution phase pyrolysis gives the 2-thiomethylquinolinone (Scheme 2.6)



Scheme 2.6 Synthesis of 2-thiomethyl substituted quinolinones

The thiomethyl group can also be displaced with other groups. Addition of Grignard reagents, both aryl and alkyl, lead to the formation of pyrolysis precursors **2.16**.¹⁷ Cyclisation in diphenyl ether gives the 2-aryl or 2-alkylquinolinones in 70 – 90% yield¹⁸ (Scheme 2.7).

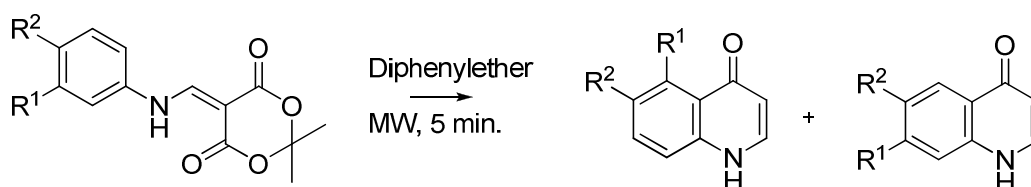


Scheme 2.7 Synthesis and pyrolysis of compound **2.16**

The regioselectivity of the electrocyclisation to form quinolinones from anilinomethylene Meldrum's acid precursors has never been studied in depth, either for solution phase or gas-phase pyrolyses.

In synthesising a library of compounds, Guy and co-workers produced a range of substituted quinolinones from anilinomethylene Meldrum's acid precursors.¹⁹ The pyrolyses were performed in solution phase under microwave heating and no yields

were given for the cyclisation reaction. The *para*- and *ortho*- substituted precursors shown no unusual reactivity, giving the 6- and 8-substituted quinolinones. For the *meta*- substituted precursors, mixtures of 5- and 7- substituted were obtained as expected and the regioselectivities are shown in table **2.1** (below).



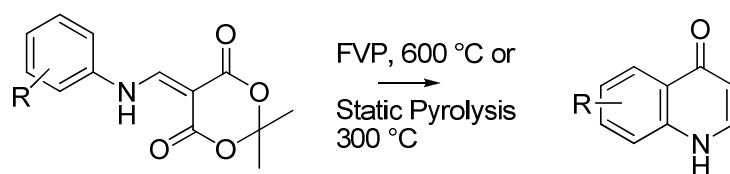
Scheme 2.8 General reaction scheme for *meta*-substituted precursors

Entry	R ¹	R ²	%5 Isomer	%7 Isomer
1	Me	H	65	35
2	F	H	50	50
3	CF ₃	H	71	29
4	PhO	H	86	14
5	MeO	MeO	74	26
6	Cl	Cl	73	27
7	Cl	Me	77	23

Table 2.1 Precursors and regioselectivities obtained by Guy *et al*¹⁹ for the pyrolysis of *meta*-substituted anilinomethylene Meldrum's acid precursors

As can be seen from table **2.1**, the regioselectivity (determined by HPLC traces) for the *meta*-substituted precursors ranges from 1:1 to 4:1, typically giving a 3:1 ratio of products. Of interest is that the major isomer reported is the more sterically hindered 5-isomer, rather than the expected 7-isomer.

Al-Awadi and coworkers reported the synthesis of quinolinones by both flash vacuum pyrolysis at 600 °C and static pyrolysis at 300 °C.²⁰ The yields and ratios (if applicable) obtained from these pyrolyses are shown below (Tables **2.2** and **2.3**)



Scheme 2.9 General reaction scheme for Meldrum's acid precursors

Entry	Substituent	Flash Vacuum Pyrolysis		
		Yield	Ratio	Notes
1	H	84	n/a	
2	<i>p</i> -Me	65	n/a	1% <i>p</i> -MeC ₆ H ₄ NH ₂
3	<i>p</i> -OMe	15	n/a	5% <i>p</i> -OMeC ₆ H ₄ NH ₂
4	<i>p</i> -NO ₂	3	n/a	10% <i>p</i> -NO ₂ C ₆ H ₄ NH ₂
5	<i>o</i> -OMe	20	n/a	2% <i>o</i> -OMeC ₆ H ₄ NH ₂ , 6% Quinolin-4-one
6	<i>o</i> -NO ₂	21	n/a	4% <i>o</i> -NO ₂ C ₆ H ₄ NH ₂ , 10% Quinolin-4-one
7	<i>m</i> -Br	33	55:45	
8	<i>m</i> -Cl	29	52:48	
9	<i>m</i> -OMe	37	54:46	
10	<i>m</i> -NO ₂	33	67:33	33% <i>m</i> -NO ₂ C ₆ H ₄ NH ₂

Table 2.2 Results obtained by Al-Awadi *et al*²⁰ for FVP of anilinomethylene Meldrum's acid precursors (Ratios are quoted as %5-Isomer:%7-Isomer for *meta*-substituted examples)

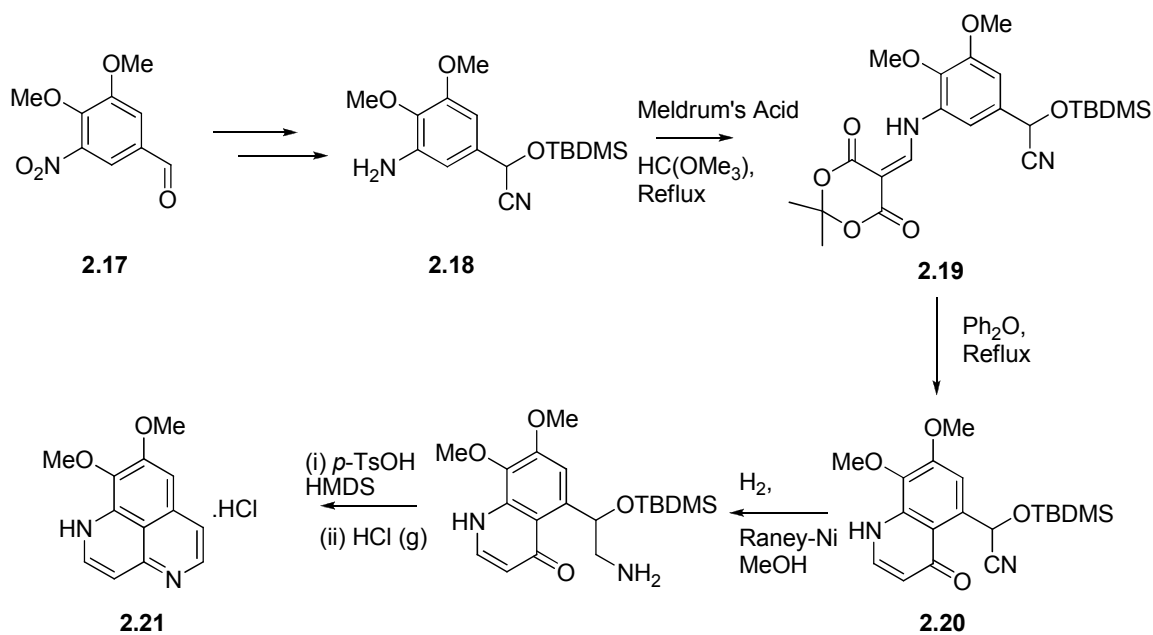
Entry	Substituent	Static Pyrolysis		
		Yield	Ratio	Notes
1	H	36	n/a	
2	<i>p</i> -Me	53	n/a	36% <i>p</i> -MeC ₆ H ₄ NH ₂
3	<i>p</i> -OMe	51	n/a	18% <i>p</i> -OMeC ₆ H ₄ NH ₂
4	<i>p</i> -NO ₂	1	n/a	12% <i>p</i> -NO ₂ C ₆ H ₄ NH ₂
5	<i>o</i> -OMe	16	n/a	18% <i>o</i> -OMeC ₆ H ₄ NH ₂ , 26% Quinolinone
6	<i>o</i> -NO ₂	n/a	n/a	No detail given
7	<i>m</i> -Br	42	67:33	
8	<i>m</i> -Cl	54	63:37	
9	<i>m</i> -OMe	22	54:46	
10	<i>m</i> -NO ₂	4	60:40	28% <i>m</i> -NO ₂ C ₆ H ₄ NH ₂

Table 2.3 Results obtained by Al-Awadi *et al*²⁰ for Static pyrolysis of anilinomethylene Meldrum's acid precursors (Ratios are quoted as %5-Isomer:%7-Isomer for *meta*-substituted examples)

As can be seen from tables **2.2** and **2.3**, the yields for both FVP and static pyrolyses are generally below 50% and can be as low as 1%. In some examples, extensive loss of the substituent is observed and significant quantities of the starting aniline are formed. With *meta*-substituted precursors, the regioselectivity is minimal, giving ratios ranging from 1:1 to 2:1, in favour of the 5-substituted quinolinone. The yields, particularly for the FVP pyrolysis experiments, are lower than those previously reported by Wentrup²¹ for example (typically around 60%) and have been revised by later work in this thesis.

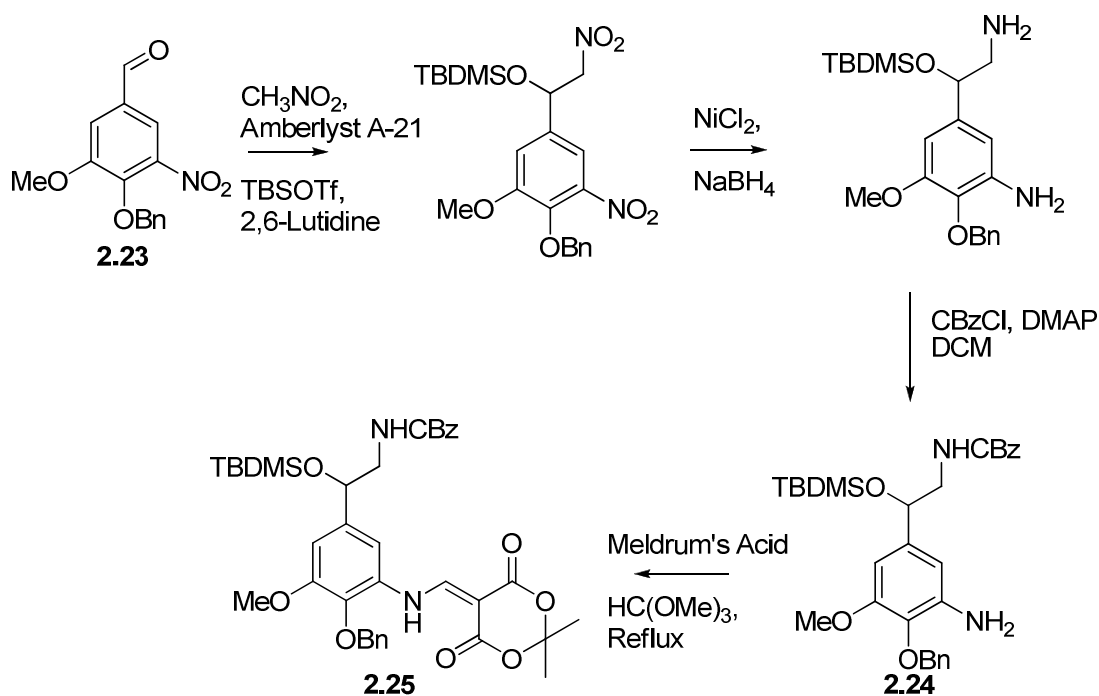
Pyrolysis of anilinomethylene Meldrum's acid derivatives has been applied to the total synthesis of natural products. One example is aaptamine, the synthesis of which starts with the dimethoxynitrobenzaldehyde **2.17**.²² This was elaborated into the substituted aniline **2.18**, which was reacted with Meldrum's acid and trimethyl orthoformate to give compound **2.19**. Thermolysis of compound **2.19** in diphenyl ether gives the quinolinone **2.20**, which in two steps can be transformed into the

hydrochloride salt of aaptamine **2.21** (Scheme 2.10).



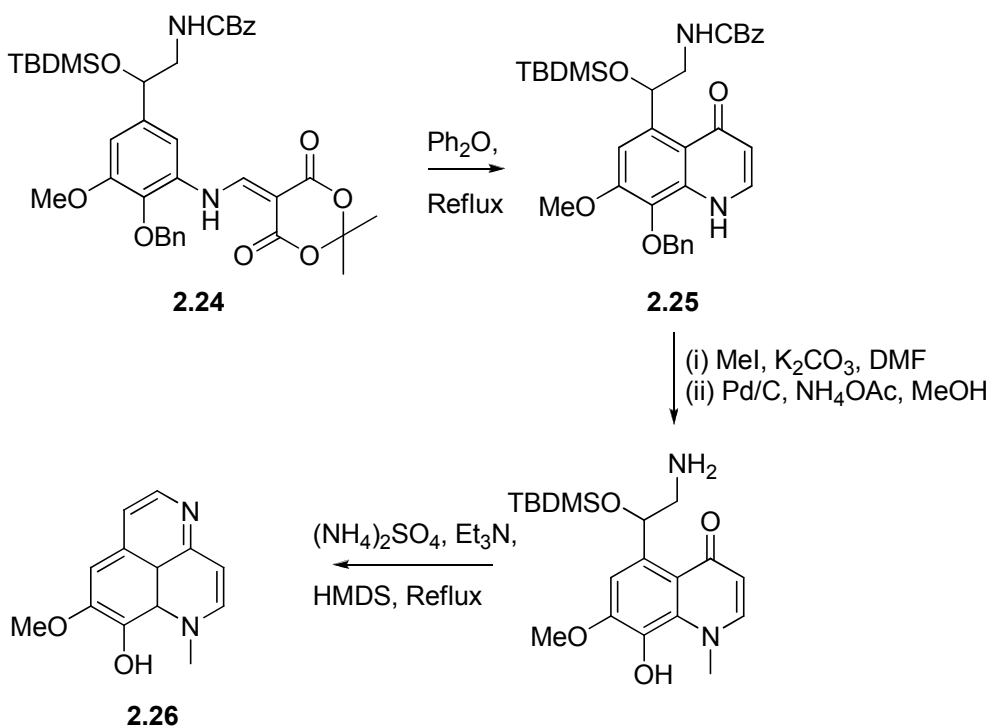
Scheme 2.10 Synthesis of aaptamine **2.21**

A similar route was employed to synthesise a related natural product, iso-aaptamine, by Sundberg.²³ Starting from the benzyl-protected compound **2.22**, addition of nitromethane to the aldehyde, reduction of the nitro groups and selective protection of the alkylamine gives the desired aniline **2.23**. Compound **2.23** was reacted with methoxymethylene Meldrum's acid to give the cyclisation precursor **2.24** (Scheme 2.11).



Scheme 2.11 Synthesis of isoaptamine precursors **2.24**

Cyclisation was effected using refluxing diphenyl ether to give the quinolinone **2.25**, which was *N*-methylated using iodomethane followed by deprotection of the alkylamine. Cyclisation of the amine using hexamethyldisilazane gave isoaptamine **2.26** (Scheme 2.12).



Scheme 2.12 Synthesis of isoaptamine **2.26**

There is also a series of pentacyclic marine natural products whose syntheses have all used quinolinone intermediates synthesised from anilinomethylene Meldrum's acid derivatives. These compounds are all related by the heterocyclic central core of the molecule (Figure 2.2).

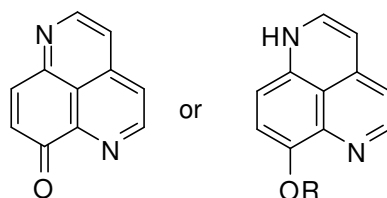
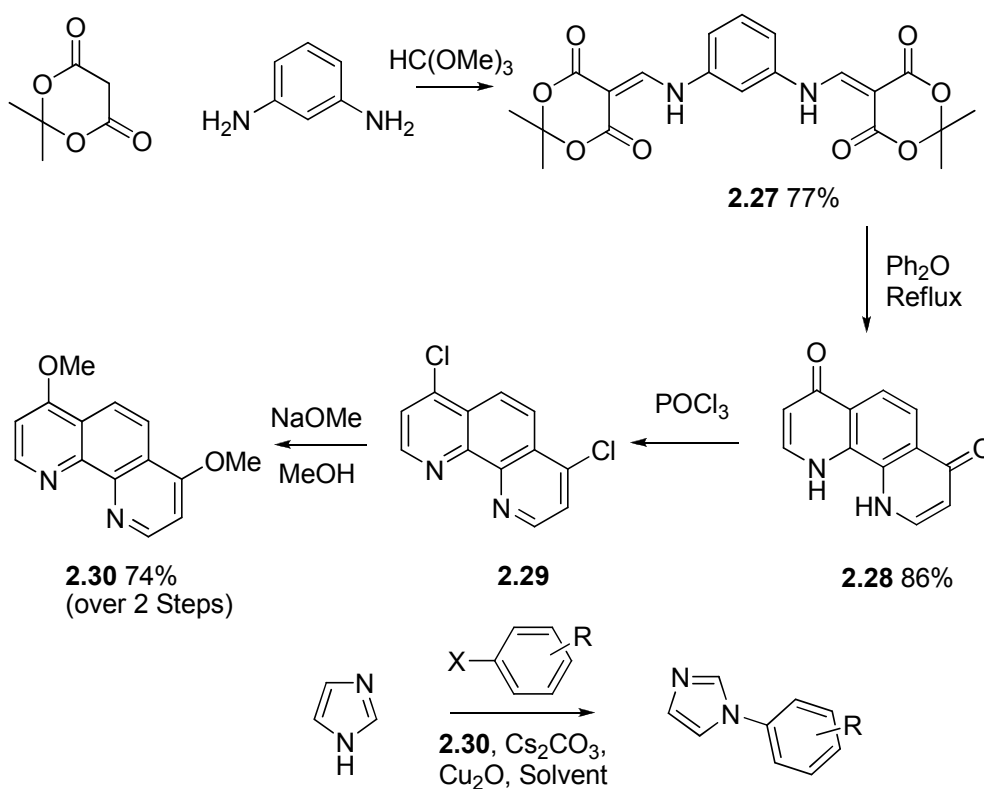


Figure 2.2 Heterocyclic core of pentacyclic marine natural products

The cyclisation reaction of anilinomethylene Meldrum's acid derivatives has been applied in the synthesis of ligands by Buchwald.²⁴ The ligand is based on a 1,10-phenanthroline ring system, which was synthesised starting from Meldrum's acid and *m*-phenylenediamine. This gives the cyclisation precursor **2.27**, which was cyclised in diphenyl ether to give the phenanthrolindione **2.28**. This was converted to the dichloride **2.29** and the chlorides displaced with sodium methoxide to give the desired ligand **2.30**. The ligand was found to be highly effective in the copper catalysed *N*-arylation reactions of imidazoles and benzimidazoles (Scheme 2.13)



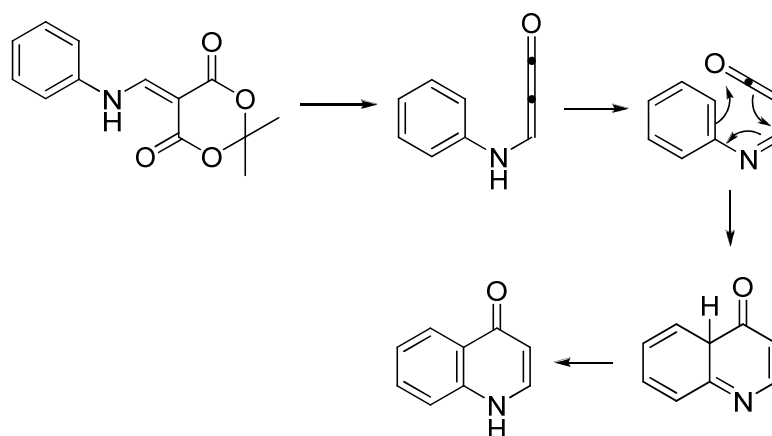
Scheme 2.13 Synthesis of ligand **2.30**

Overall, the pyrolysis of anilinomethylene Meldrum's acid precursors has been used widely as a synthetic route to quinolin-4-ones in both solution and gas phases. These have seen wide range of applications, However no in-depth study on the effect of substituents, in either the *ortho* or *meta* positions on the regioselectivity of the cyclisation has been performed.

2.2 Discussion

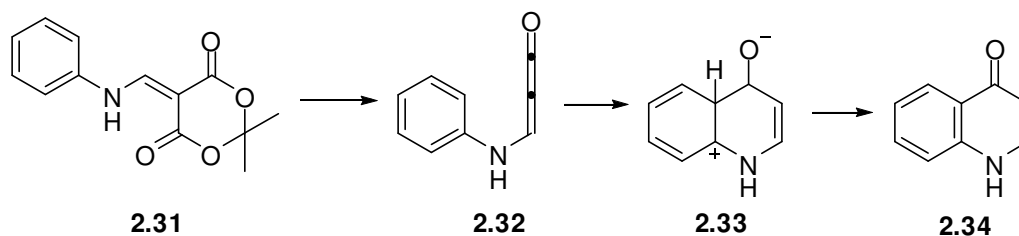
2.2.1 Mechanism of the Reaction

Quinolinones are typically synthesised from anilinomethylene derivatives of Meldrum's acid in solution phase, but can also be synthesised in the gas-phase by flash vacuum pyrolysis. The typically accepted mechanism is shown in scheme 2.14.^{21,25}



Scheme 2.14 Mechanism for the formation of quinolinones from anilinomethylene Meldrum's acid precursors

Al-Awadi and coworkers reported the synthesis of quinolin-4-ones from Meldrum's acid derivatives similar to the work described in this chapter.²⁰ The proposed mechanism for the cyclisation is shown in scheme 2.15 below.



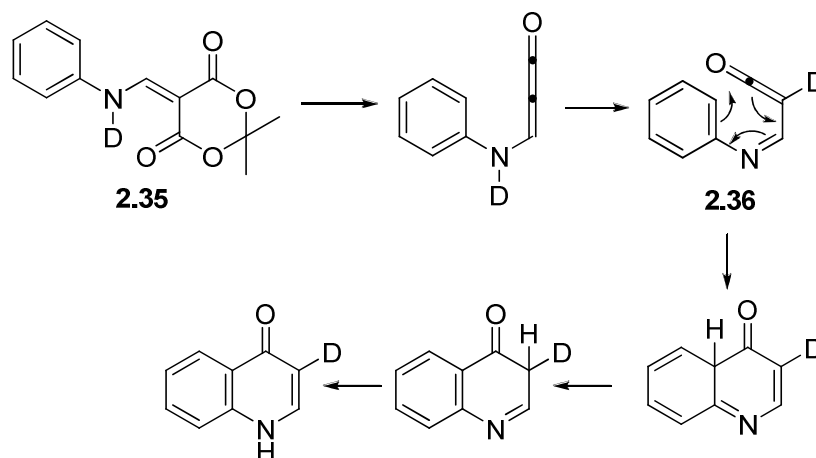
Scheme 2.15 Mechanism proposed by Al-Awadi *et al*²⁰

The Meldrum's derivative loses acetone and carbon dioxide to give the methylene ketene 2.32. This undergoes cyclisation to generate a species shown as the dipolar

intermediate **2.33** with undefined bonding at C3 and C4, which then in an unspecified mechanism rearranges to the final product **2.34**. It was also reported that this cyclisation is dependent on the electronic properties, with electron-withdrawing groups ‘decreasing the nucleophilicity of the ring’ and leading to decomposition of the methyleneketene. However, it should also be noted that both electron donating groups (OMe) and electron-withdrawing groups (NO₂) were reported to give similar yields (generally >20%), with significant amounts of recovered anilines (5-20%).

This mechanism is at odds with matrix isolation studies by Wentrup,²¹ which have shown that at -198 °C two absorptions in the IR spectrum can be observed. One corresponds to the methyleneketene (2079 cm⁻¹) and the other was assigned to the imidoyl ketene (2123 cm⁻¹).

In the present work, two approaches were utilised to probe the mechanism. The first was to pyrolyse an *N*-deuteriated precursor **2.35** (Scheme 2.16)

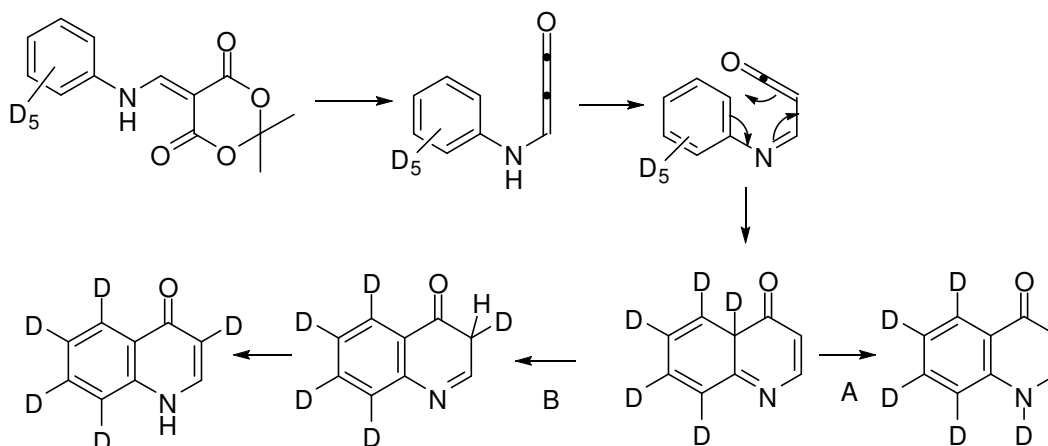


Scheme 2.16 Proposed mechanism for the pyrolysis of *N*-deuteriated precursors **2.35**

If the mechanism proposed by Wentrup²¹ is correct, then the deuterium should undergo the 1,3 shift to give the imidoylketene **2.36**. The result of this should be observable by a lack of a signal (or a reduction in its intensity) for the proton in 3-position in the ¹H NMR spectrum.

The second approach is to start with a deuteriated aromatic ring. This experiment determines how the proton in the aromatic ring shifts onto the nitrogen atom. Once

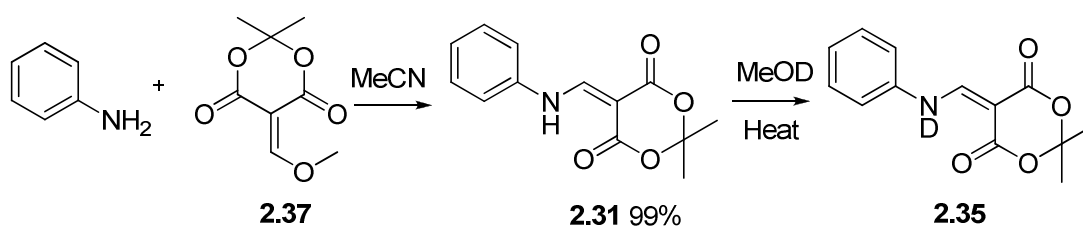
the cyclised intermediate has been formed, two possible mechanisms are possible (Scheme 2.17).



Scheme 2.17

Pathway A involves a direct 1,3-shift of the deuterium from the ring junction to the nitrogen atom. However such shifts are disallowed suprafacially and cannot occur antarafacially for this ring system by an intramolecular mechanism, but should this occur at high temperature, the atom at the 3-position should be mainly protium. Pathway B involves an allowed 1,5 shift to the 3-position, which restores the aromaticity of the benzene ring, followed by a disallowed 1,3 shift. Disallowed shifts may occur by intermolecular mechanism(s) e.g. in the solid phase as suggested by Wentrup.²⁶ Due to isotope effects, protium should undergo the disallowed shift preferentially, leaving the 3-position mainly deuterium.

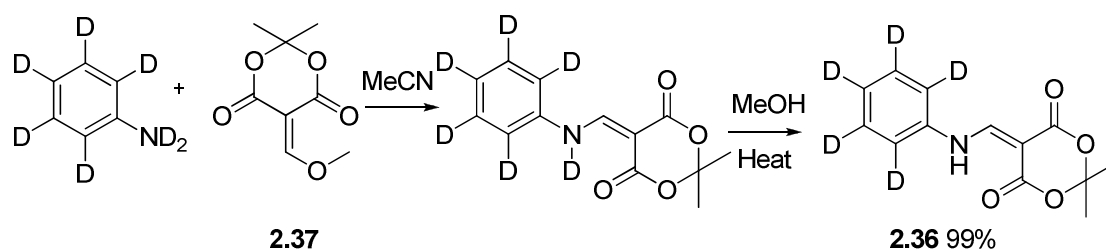
The *N*-deuterium labelled product was synthesised from the NH compound, itself synthesised from aniline and methoxymethylene Meldrum's acid **2.37**. Heating compound **2.31** in methanol-OD and then quickly removing the methanol under high vacuum gave the ND compound **2.36** (Scheme 2.18).



Scheme 2.18 Synthesis of compound **2.35**

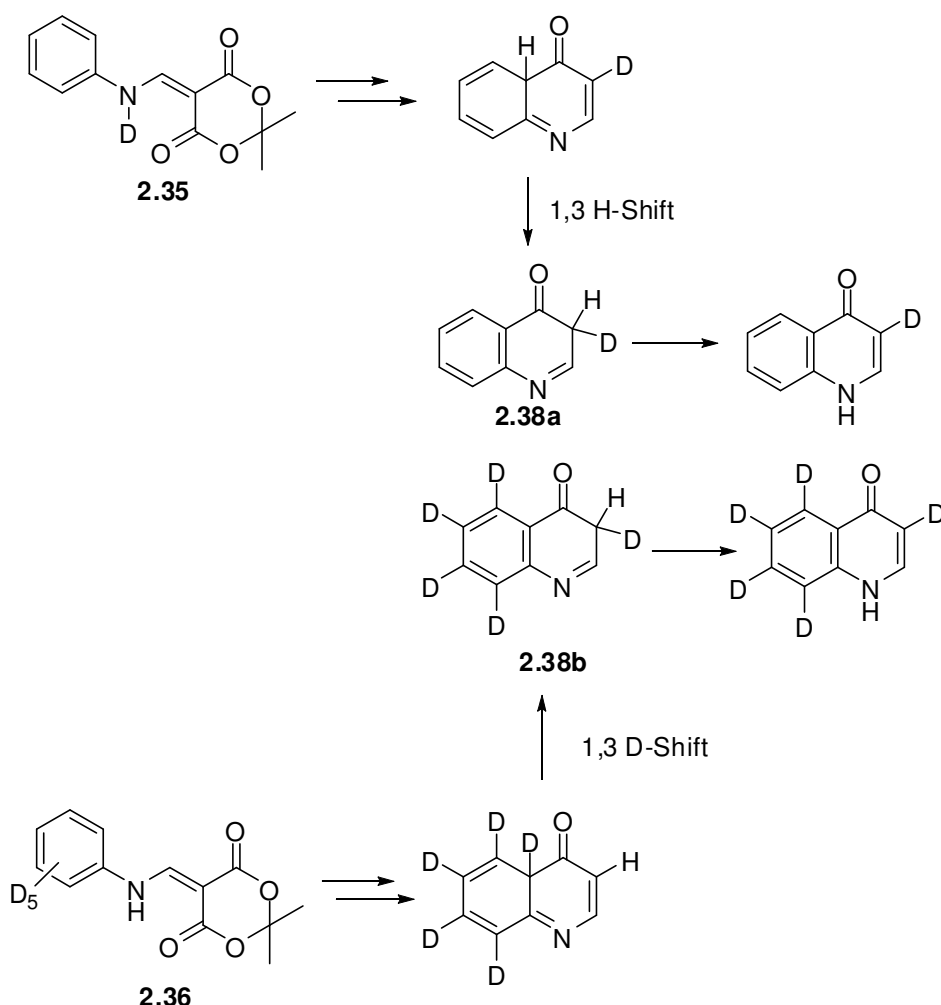
Pyrolysis of the *N*-D labelled compound **2.35** was performed at 500 °C and the pyrolysate dissolved in *d*₆-DMSO. The ¹H NMR spectrum of the crude pyrolysate showed the signal at $\delta = 6.1$ ppm to be reduced by 73%, corresponding to 73% incorporation of deuterium into the 3-position of the quinolinone. These results support the matrix isolation work by Wentrup and shows that the formation of the imidoylketene occurs, but the incorporation in the 3-position was less than 100%, due to the isotope effect of the final 1,3 hydrogen shift.

The deuteriated aromatic ring precursor was synthesised from *d*₇-aniline and methoxymethylene Meldrum's acid to give a *d*₆-precursor. Heating the *d*₆ precursor in methanol exchanged the *N*-deuterium for hydrogen to give the desired *d*₅ compound **2.36** in 99% yield (Scheme 2.19).



Scheme 2.19 Synthesis of compound **2.36**

Pyrolysis of compound **2.36** at 500 °C and dissolution of the pyrolysate in *d*₆-DMSO showed the expected two signals in the ¹H NMR spectrum. The proton in the 3-position showed a reduction in the measured integral by 73%. This also estimates the incorporation of deuterium to be 73% (the results are consistent with an isotope effect of approximately 2.1 [± 0.6]) and shows that the 1,5 hydrogen shift occurs. The percentage of deuterium incorporated in the product is comparable with that of the pyrolysis of *N*-deuteriated precursor **2.35**, which shows that they proceed *via* intermediates **2.38a** and **2.38b**, which must undergo comparable 1,3 hydrogen shifts (Scheme 2.20)



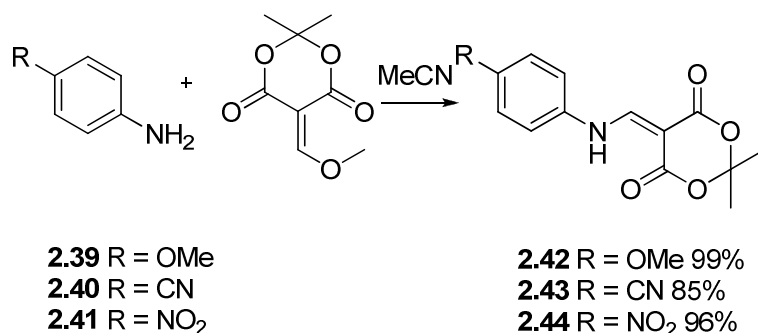
Scheme 2.20 Mechanisms for the pyrolysis of compounds **2.35** and **2.36**

It has been widely known that these types of cyclisation also work in solution phase, using high boiling solvents (typically Dowtherm A).¹² It may also be possible that in solution phase, an alternative intermolecular mechanism may occur for the hydrogen shift(s). The d_5 -precursor **2.36** was heated in Dowtherm A for 20 min and the product collected by precipitation with light petroleum. The ^1H NMR spectrum of the resulting product showed only a 35% incorporation of deuterium into the 3-position. The indication of this result is that there are intermolecular processes occurring (allowing direct loss of deuterium from C4a prior to the 1,5-shift), that happen at a faster rate than the 1,5 shift. The result of this is to lower the percentage of incorporation of deuterium in the 3-position of the product.

Another issue raised in the work by Al-Awadi was the effect of substituents,²⁰ which were said to alter the “nucleophilicity of the ring carbons”. Based on this argument,

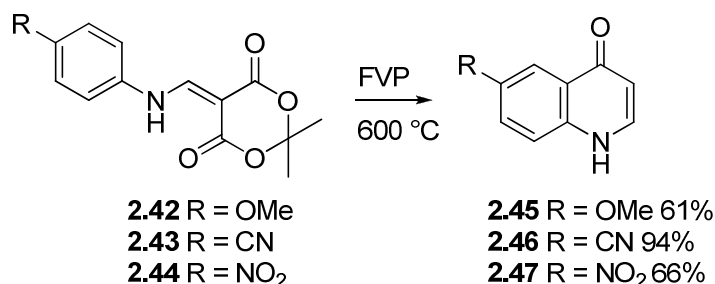
the electron-withdrawing groups (such as NO₂) lower the nucleophilicity and lower the reaction yield, while electron donating groups (such as OMe) should give higher yields. However the yields of the pyrolysis were generally very low (e.g. 15% for *p*-OMe and 3% *p*-NO₂) for most substituents which makes it hard to observe any general trend from the data reported.

In order to study the electronic properties of the substituent, *para* substituents were chosen to minimise the steric effects of the substituent. Methoxy- and nitro-groups were chosen to be repeated. Due to the known pyrolysis chemistry of the nitro group²⁷ and that nitro-containing precursors can be poorly volatile (leading to high inlet temperatures and extensive decomposition in the solid state), a second electron-withdrawing group was chosen, a cyano- group. As before, the precursors **2.42** – **2.44** were synthesised from the *para*-substituted anilines **2.39** – **2.41** and methoxymethylene Meldrum's acid **2.38** in excellent yields (Scheme 2.21).



Scheme 2.21 Synthesis of compounds **2.42** – **2.44**

The pyrolyses were carried out at 600 °C and the products were isolated by removal from the trap by suspension in acetone. The acetone was removed and the product recrystallised as necessary (Scheme 2.22)



Scheme 2.22 Pyrolysis of compounds **2.42** – **2.44**

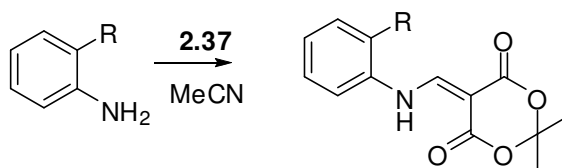
The *p*-methoxy precursor **2.42** gave 6-methoxyquinolinone **2.45** in 61% yield after recrystallisation from methanol, in comparison to the reported result of 15% yield with 5% of recovered *p*-anisidine. The *p*-cyano compound **2.43** gave 6-cyanoquinolinone **2.46** in 94% yield, sufficiently pure for further use. The *p*-nitro compound **2.44** gave 6-nitroquinolinone **2.47** in 66% yield, compared to the reported 3% yield with 10% recovered *p*-nitroaniline.

The implication of the above results is that the electronic nature of the substituents has little effect on whether a substrate is going to cyclise efficiently or not. Also the yields obtained for the FVP experiments were significantly higher than the results obtained by Al-Awadi.²⁰

2.2.2 *Ortho*-Substituted Amines to 8-Substituted Quinolinones

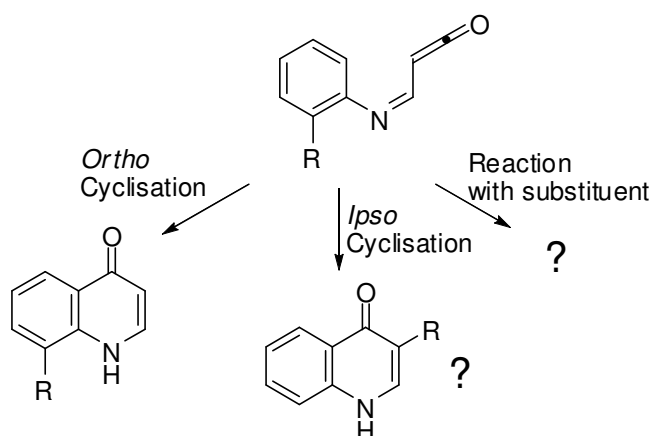
2.2.2.1 Introduction

No in-depth study of substituent effects on the cyclisation of precursors based on *ortho*-substituted anilinomethylene Meldrum's acid derivatives has been performed. These compounds are derived from *ortho*-substituted anilines and methoxymethylene Meldrum's acid **2.37** (Scheme 2.23)



Scheme 2.23 Synthesis of *ortho*-substituted anilinomethylene Meldrum's acid precursors

With these precursors, a number of reactions are possible. Cyclisation can occur *meta* to the substituent to give the 8-substituted product or potentially at the *ipso* position, though whether the group then subsequently undergoes a sigmatropic shift (to give the 3-substituted quinolinone) or not was unknown. Finally the group may react with the ketene in some alternative fashion (Scheme 2.24).



Scheme 2.24 Possible reactions of *ortho*-substituted imidoalkenes

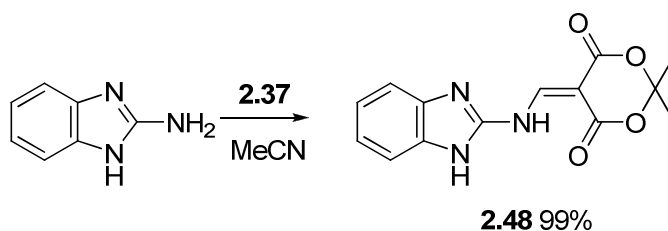
The substituents chosen could be separated into a number of groups, shown in table 2.4 (below)

Group	Substituents
Alkyl	Me*, Et
Halogen	F, Cl, Br, I
Group 6 Substituents	OH, OMe, OAc, SH
Electron-withdrawing Groups	CN, NO ₂ , CF ₃ , CO ₂ Me*, CONH ₂ , Ac*

Table 2.4 Groups of substituents chosen for the study of the effect of substituents on the pyrolysis of *ortho*-substituted anilinomethylene Meldrum's acid precursors

*work previously performed by Dr. A. P. Gaywood.²⁸

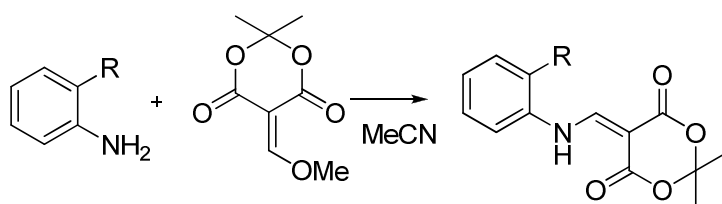
A system based on 2-aminobenzimidazole was also chosen. The Meldrum's acid derivative of 2-aminobenzimidazole has been previously synthesised but was reported to be involatile under FVP conditions. Addition of methoxymethylene Meldrum's acid **2.37** to a solution of 2-aminobenzimidazole gave compound **2.48** in 99% yield (Scheme 2.25).



Scheme 2.25 Synthesis of compound **2.48**

2.2.2.2 Synthesis of Starting Materials

The precursors were synthesised from the appropriately substituted aniline (all but one of which are commercially available) and methoxymethylene Meldrum's acid. The acetoxy compound **2.56** was synthesised by acetylation of the hydroxy compound **2.54**, using acetyl chloride and triethylamine, in quantitative yield. The yields are given below, with the general reaction scheme (Scheme 2.26, Table 2.5)



Scheme 2.26 General reaction scheme for the synthesis of *ortho*-substituted anilinomethylene Meldrum's acid precursors

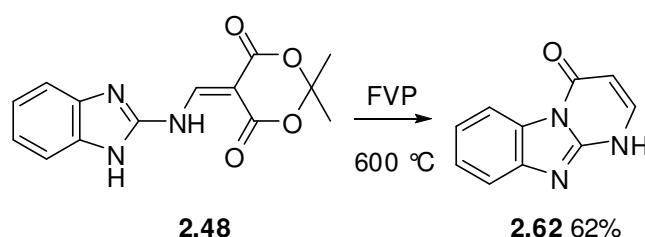
Group	Substituent	Compound No.	Yield /%
Alkyl	Et	2.49	99
Halogen	F	2.50	95
	Cl	2.51	99
	Br	2.52	99
	I	2.53	99
Phenol	OH	2.54	92
	OMe	2.55	99
	OAc	2.56	99
	SH	2.57	90
EWG	CN	2.58	99
	NO ₂	2.59	95
	CF ₃	2.60	99
	CONH ₂	2.61	99

Table 2.5 Yields for the synthesis of *ortho*-substituted anilinomethylene Meldrum's acid precursors **2.49** – **2.61**

2.2.2.3 Pyrolysis of Meldrum's acid derivatives

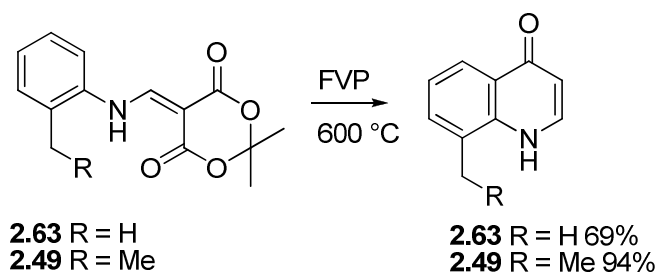
Compounds **2.49** – **2.61** were pyrolysed under FVP conditions to give the product(s). Typically the pyrolysis experiment was carried out on a small scale (*ca.* 50 mg) and the product(s) were dissolved in *d*₆-DMSO for analysis. The reactions were then scaled up and the products isolated from the reaction mixture.

Pyrolysis of the 2-aminobenzimidazole compound **2.48** gave a yellow solid. No extensive decomposition of the starting material in the inlet tube was observed. Recrystallisation of the crude pyrolysate from methanol gave compound **2.62** in 62% yield (Scheme 2.27). Previous attempts at the synthesis of compound **2.62** by Al-Awadi *et al*²⁰ in the gas phase were unsuccessful, due to difficulties in the volatisation of compound **2.48**



Scheme 2.27 Pyrolysis of compound **2.48**

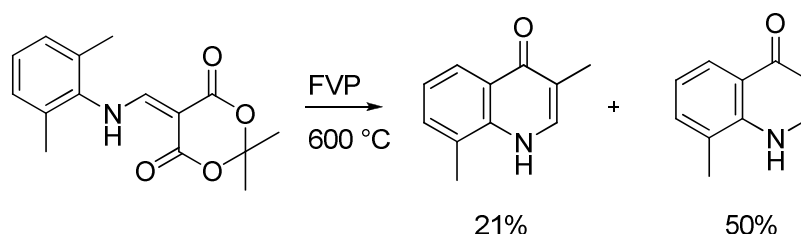
Previous work has shown that the methyl substituted compound **2.63** gives 8-methylquinolinone **2.64** in 69% yield. Similarly the ethyl analogue **2.49** gives 8-ethylquinolinone **2.65** in 94% yield (Scheme 2.28).



Scheme 2.28 Pyrolysis of compounds **2.63** and **2.49**

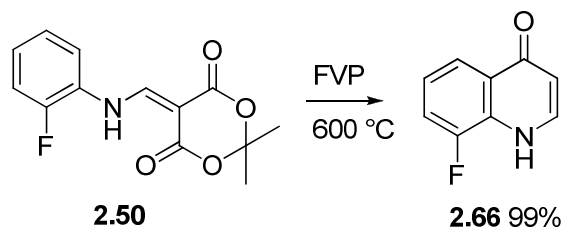
Alkyl groups demonstrate no unusual reactivity in this cyclisation and only give 8-

substituted quinolinones. 2,6-Dialkyl precursors have been shown to give 3,8-dialkyl products²⁸ (with significant amounts of the 8-monosubstituted product), but this shows that the alkyl groups will only migrate when cyclisation must occur on a substituted site (Scheme 2.29).



Scheme 2.29 Pyrolysis of the 2,6-dimethylaniline derivative

Of the halogens, only the fluoro and chloro compounds **2.50** and **2.51** gave clean pyrolyses. The pyrolysis of bromo and iodo compounds **2.52** and **2.53** gave complex mixtures of products, with no easily identifiable products. The fluoro compound upon pyrolysis gave a single product as a white solid. The ¹H NMR spectrum of the product was consistent with the structure of 8-fluoroquinolinone **2.66** (Scheme 2.30).



Scheme 2.30 Pyrolysis of compound **2.50**

Pyrolysis of the chloro compound **2.51** gave a brown solid, isolated in 30% yield. The ¹H NMR spectrum of the compound however did not have the typical doublet at $\delta_H = 6.0 - 6.2$ ppm, due to the proton in the 3-position (Figure 2.3).

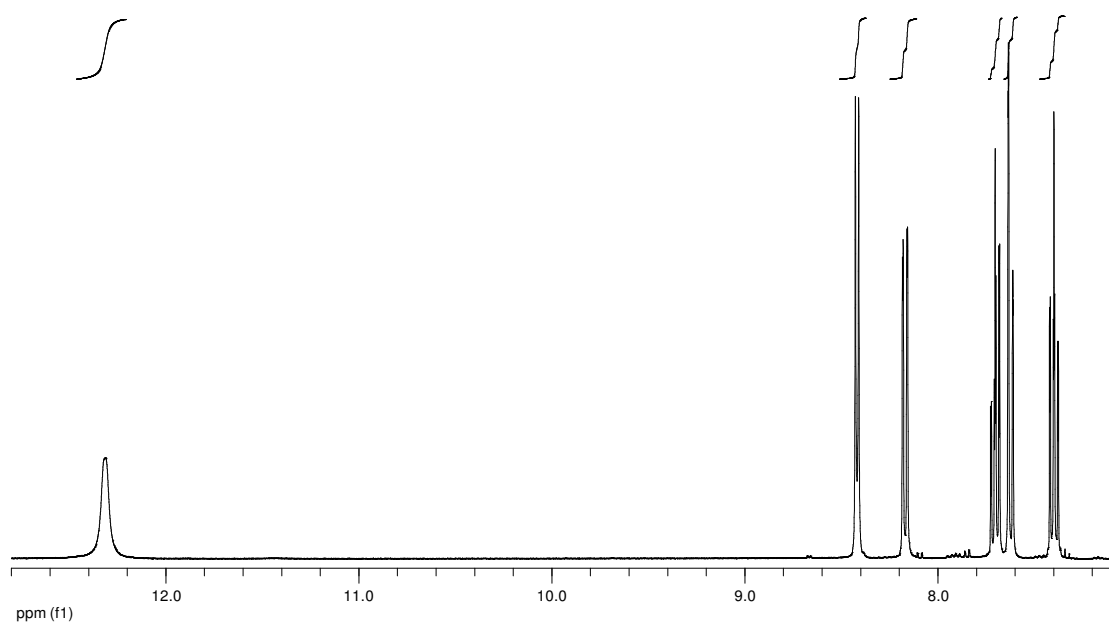


Figure 2.3 ^1H NMR spectrum of the product from the pyrolysis of chloro compound **2.51**

A COSY experiment was performed in order to discover the relationship between the protons (Figure 2.4)

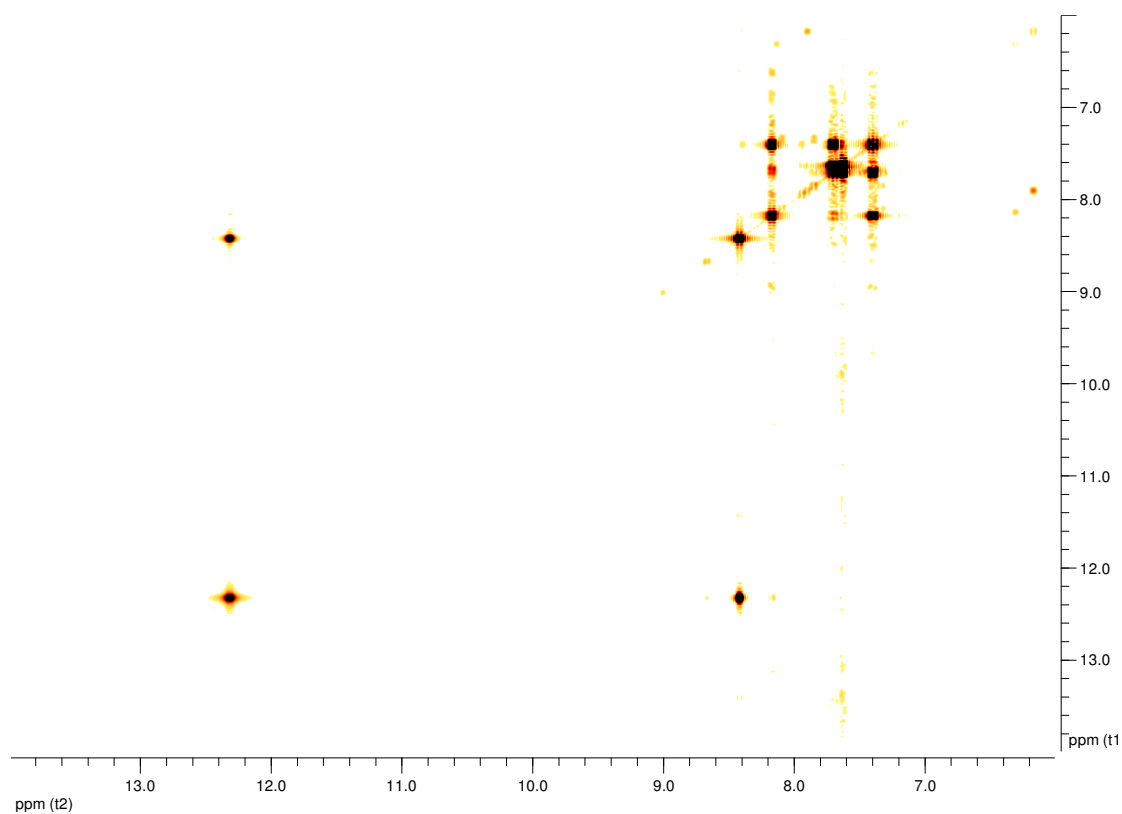


Figure 2.4 COSY spectrum of the product from the pyrolysis of chloro compound **2.51**

From figure 2.4, we can see that the proton at $\delta_H = 8.4$ ppm couples to the NH proton at $\delta_H = 12.3$ ppm, which identifies it as the proton in the 2-position. This proton shows no further COSY signals. The proton at $\delta_H = 8.3$ ppm shows a correlation to the proton at $\delta_H = 7.3$ ppm, which in turn shows a correlation to the proton at $\delta_H = 7.7$ ppm. The proton at $\delta_H = 7.7$ ppm shows a correlation to the proton at $\delta_H = 7.6$ ppm and identifies these four protons as being in the same spin system. With this pattern, the only possible structure for the product was 3-chloroquinolinone **2.67** (Figure 2.5).

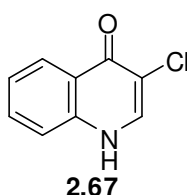
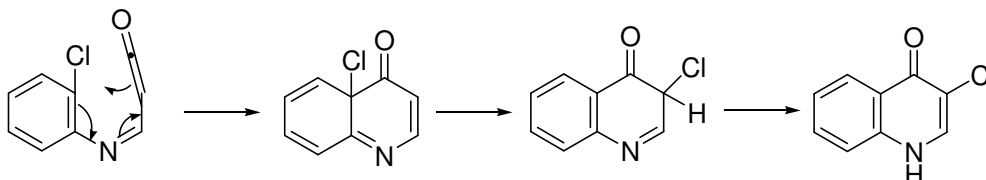


Figure 2.5 Structure of 3-chloroquinolinone **2.67**

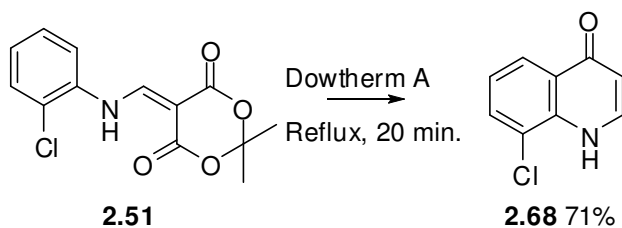
This must arise from *ipso* cyclisation and a 1,5 sigmatropic shift of the chlorine atom to the 3-position, followed by 1,3-shift of the 3-hydrogen to the nitrogen atom (Scheme 2.31).



Scheme 2.31 Mechanism for the formation of 3-chloroquinolinone **2.67**

The implication is that in the gas phase the aptitude for a chlorine atom to undergo sigmatropic shifts is higher than that for hydrogen in this system.

Solution-phase pyrolysis, under microwave heating, of compound **2.51** has been reported in the literature to give 8-chloroquinolinone rather than the 3-chloroquinolinone obtained by FVP.¹⁹ Using conventional heating methods, solution-phase pyrolysis of compound **2.51** in Dowtherm A gave 8-chloroquinolinone **2.68** in 71% yield (Scheme 2.32).



Scheme 2.32 Solution phase pyrolysis of compound **2.51**

The implication of this result is that the solution phase pyrolysis has an alternative mechanism to the 1,5 hydrogen shift, most likely an intermolecular process, that allows the 8-chloro compound to be formed over the 3-chloro product. In the gas-phase this cannot occur, leading to the 3-chloro product.

DFT calculations at B3LYP/6-31G** level were employed to model the reaction that forms 3-chloroquinolinone **2.67**. The energy surface obtained is shown below (Figure 2.6)

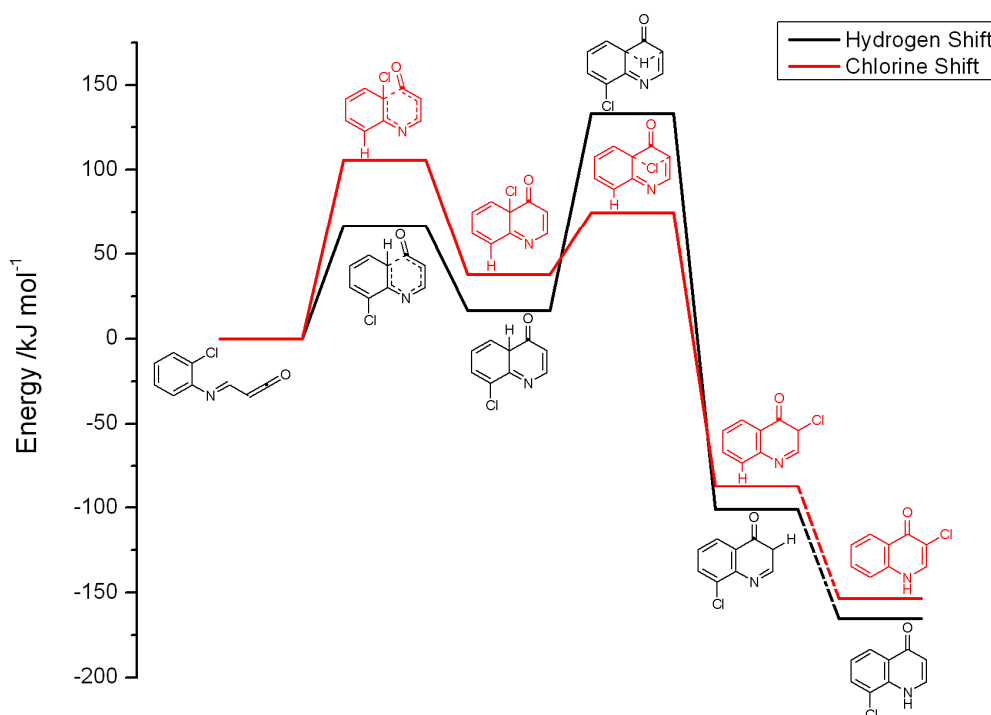
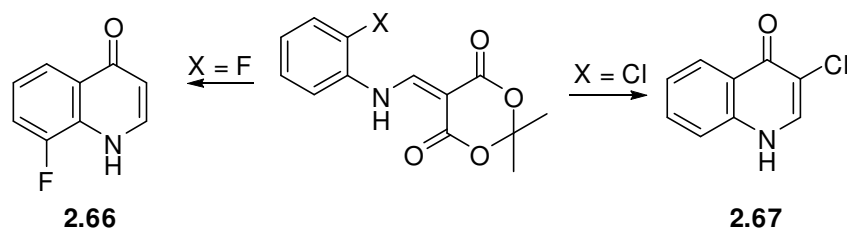


Figure 2.6 Energy surface for the formation of 3- and 8-chloroquinolinones

From figure 2.6, it can be seen that the initial cyclisation reaction is higher in energy for the *ipso* cyclisation than for the *meta* cyclisation (105.7 vs 66.7 kJ mol⁻¹). However for the 1,5 sigmatropic shift, the energy of the chlorine migration is

significantly lower than that for the hydrogen migration (36.9 vs 116.3 kJ mol⁻¹). This explains why the migration occurs in the gas-phase but not in solution phase, since in solution phase the reaction can follow the initial *meta* cyclisation, which is lower in energy, and then an intermolecular process allows the higher energy hydrogen migration to be circumvented.

One aspect of the *ortho*-halogen pyrolyses is why chlorine undergoes a 1,5 sigmatropic shift to give 3-chloroquinolinone, while fluorine does not (Scheme 2.33)



Scheme 2.33 Pyrolysis of *ortho*-halogenoanilinomethylene Meldrum's acid derivatives

To understand this result, the fluorine energy surface was modelled at B3LYP/6-31G** level (Figure 2.7)

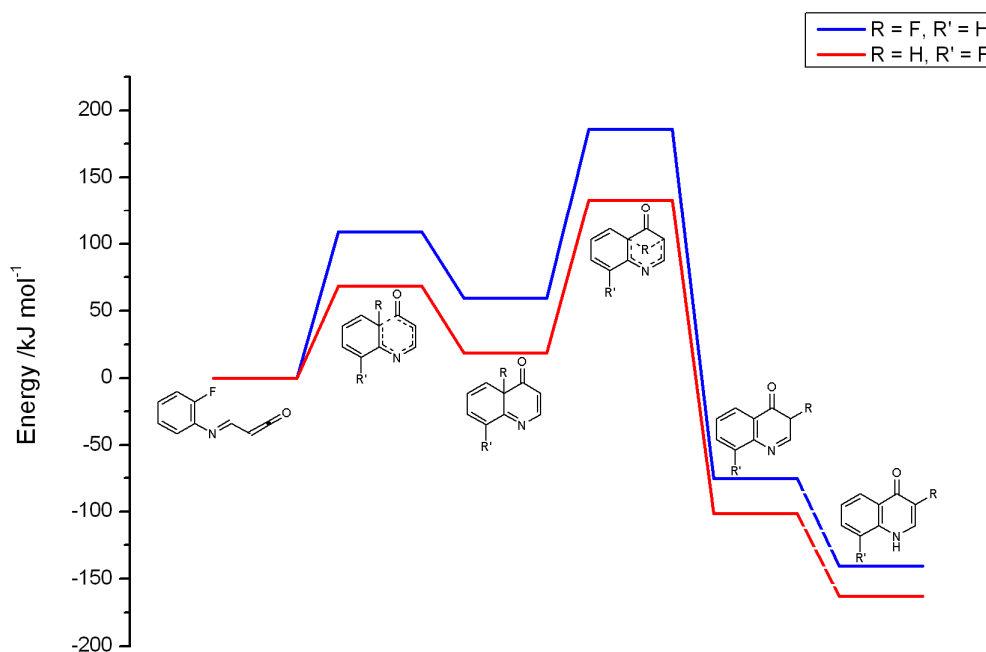
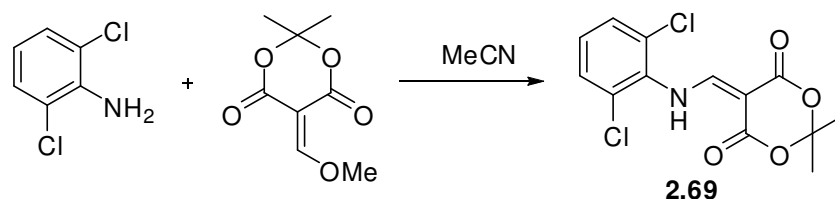


Figure 2.7 Energy surfaces for the formation of 3- and 8-fluoroquinolinones

From figure 2.7, the energy surface for the *meta*-cyclisation and 1,5-hydrogen shift

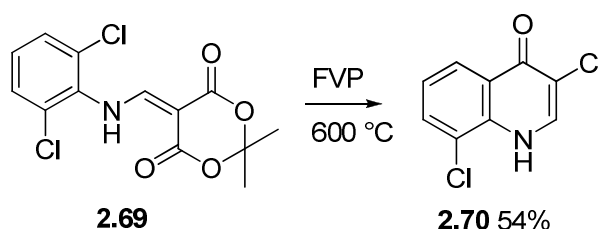
(red in figure 2.7) is lower in energy than the *ipso*-cyclisation and fluorine migration (blue in figure 2.7). Comparing the fluorine and chlorine energy surfaces, the energies of the 1,5-halogen sigmatropic shifts are different, with a smaller barrier for the chlorine shift (36.9 kJ mol⁻¹ for Cl vs. 126.5 kJ mol⁻¹ for F).

As a further example of the migration of chlorine atoms, the 2,6 dichloro compound **2.69** was synthesised from 2,6-dichloroaniline and methoxymethylene Meldrum's acid in 91% yield (Scheme 2.34)



Scheme 2.34 Synthesis of compound **2.69**

Pyrolysis of compound **2.69** at 600 °C gave a brown solid, which was identified as 3,8-dichloroquinolinone **2.70** from its ¹H NMR spectrum in 54% yield (Scheme 2.35).

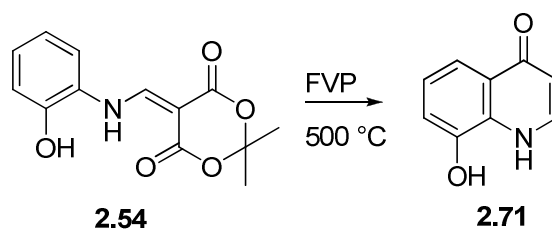


Scheme 2.35 Pyrolysis of compound **2.69**

The migratory aptitudes of specific groups in this system are discussed later in this chapter.

Pyrolysis of 2-aminophenol derived compound **2.54** lead to the formation of a yellow solid, whose ¹H NMR spectrum showed the presence of two products. The two products showed different solubilities in organic solvents and the more soluble product was separated from the other by distilling hot chloroform over the pyrolysate. The insoluble white solid was removed from the U-tube by suspension in acetone and was identified as 8-hydroxyquinolinone **2.71** by comparison with literature data,²⁹

isolated in 33% yield (Scheme 2.36)



Scheme 2.36 Synthesis of 8-hydroxyquinolinone **2.71**

The ^1H NMR spectrum of the other product showed that it was not a quinolinone by the presence of a doublet at $\delta_H = 4.98$ ppm, lower than the typical chemical shift of the 3-proton in a quinolinone. The mass spectrum of the compound showed it to have a molecular weight of 161, isomeric with 8-hydroxyquinolinone. A COSY experiment was performed to show the relationship between the protons in the molecule (Figure 2.8)

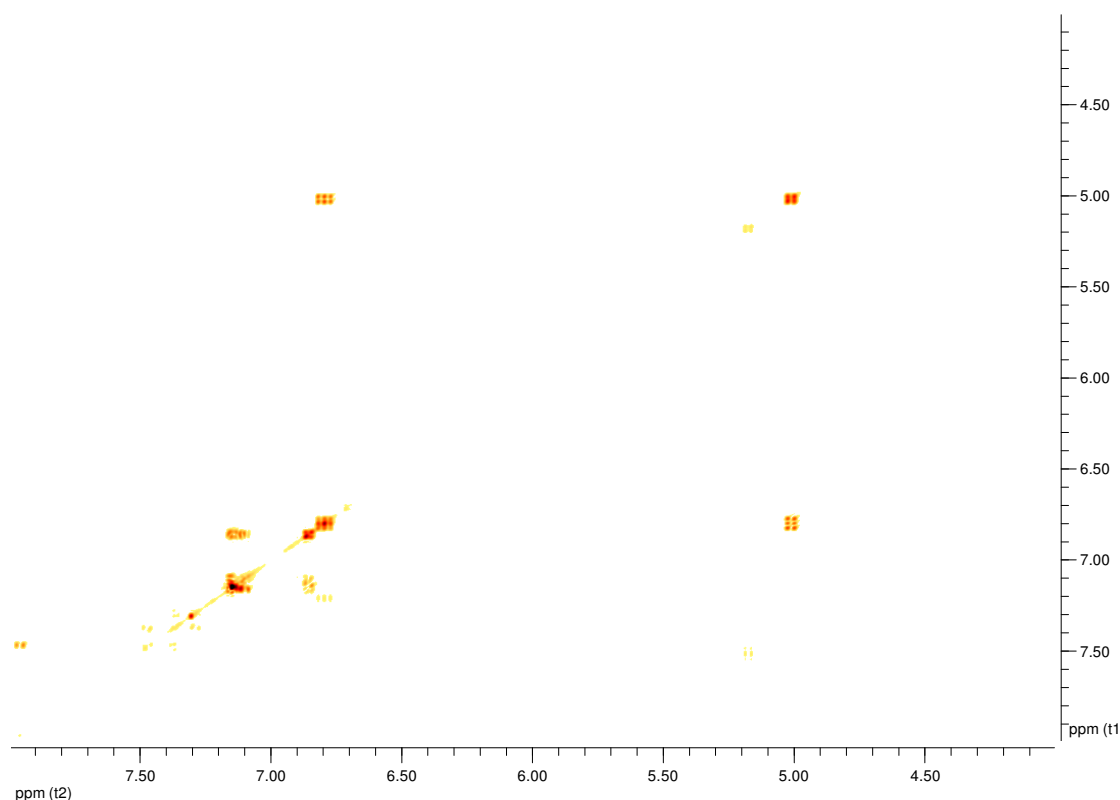


Figure 2.8 COSY spectrum of compound **2.72**

From figure 2.8, we can see the doublet at $\delta_H = 4.9$ ppm is related to the proton at δ_H

= 6.77 ppm and both show no further COSY signals. The chemical shift of the lower proton at $\delta_H = 4.9$ ppm hints at the proton being next to a carbonyl group in a push-pull system, while the other proton at $\delta_H = 6.77$ ppm hints at being next to the nitrogen atom. The proton at $\delta_H = 6.83$ ppm coupling with the three proton multiplet at $\delta_H = 7.1$ ppm, implying a four proton aromatic ring system. The ^{13}C NMR spectrum showed the presence of three quaternary carbons and 6 CH atoms, with one of the quaternary carbons at $\delta_C = 165.69$ ppm indicating the presence of a carbonyl. A plausible structure for the product is 1,5-benzoxazepin-4-one **2.72**, isolated in 40% yield (Figure 2.9).

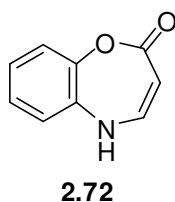
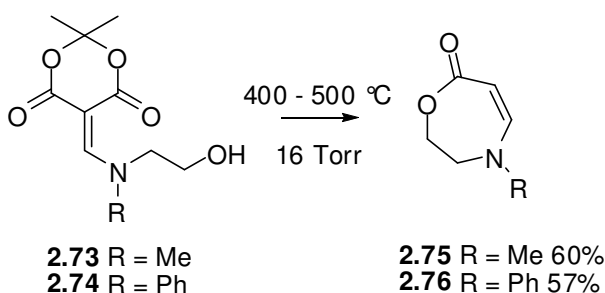


Figure 2.9 Structure of 1,5-benzoxazepin-4-one **2.72**

This structure fits with the NMR data of the compound **2.72** obtained. Only a small number of reports of 1,5-benzoxazepinones have been reported in the literature, with compound **2.72** unknown in the literature. Pommelet *et al* reported the synthesis of oxazepinones **2.75** and **2.76** by pyrolysis of the precursors **2.73** and **2.74**, in yields of ca. 60% (Scheme 2.37).^{29,30}



Scheme 2.37 Synthesis of oxazepinones **2.75** and **2.76**

The ^1H NMR spectrum of the products were reported to show peaks at around 4.6 ppm and 6.8 ppm for the 2- and 3-positions of the benzoxazepinone ring respectively, with coupling constants of around 9 Hz.²⁹ These figures are comparable to those obtained for compound **2.72**. They also reported that thermolysis of compound **2.54**

under flow conditions at 500 °C gave 8-hydroxyquinolinone as the sole product in 80%.

Although a crystal structure of compound **2.72** was not obtained, a gas phase structure was calculated at MP2/6-31G** level. This calculated structure is shown below (Figure 2.10)

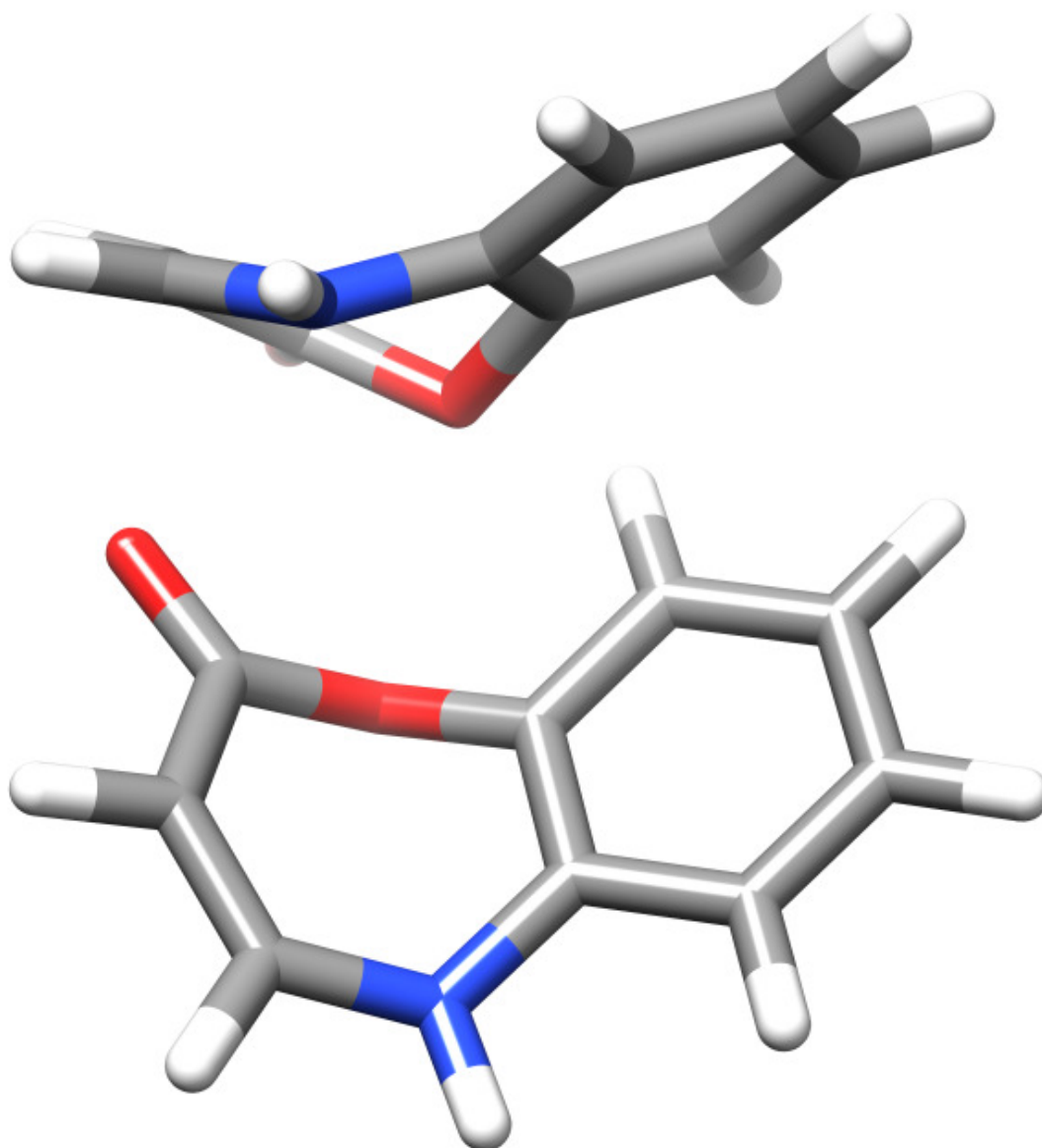
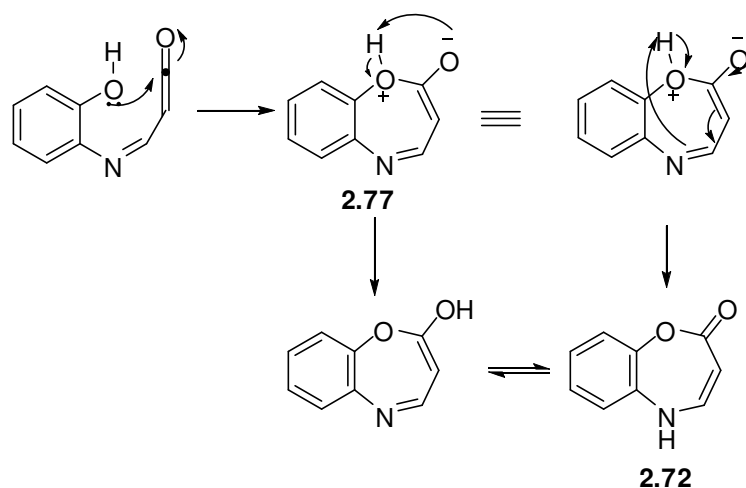


Figure 2.10 Calculated gas phase structure of compound **2.72**

From figure 2.10, the 7-membered ring of compound 2.72 is not flat and bends at the ester carbonyl group. The push-pull system is also not planar and is slightly twisted. This may be partially disrupting the conjugation through the push-pull system and

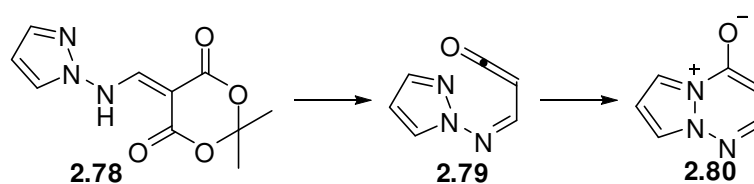
effect the chemical shift of the two protons in the system.

The mechanism for the formation of compound **2.72** may involve the lone pair on the hydroxyl group undergoing addition to the ketene to generate the intermediate **2.77**. The final hydrogen shift can take place in one step or *via* the hydroxy- tautomer to give the product (Scheme **2.38**).



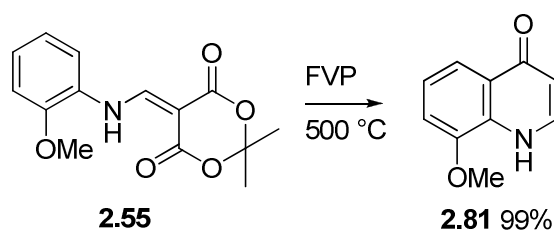
Scheme 2.38 Mechanism for the formation of compound **2.72**

Dipolar structures related to **2.77** are known in the literature,³¹ for example pyrolysis of *N*-aminopyrazole derived compound **2.78** gives the imidoalkyne **2.79**, which then cyclises to give betaine **2.80** (Scheme **2.39**)



Scheme 2.39 Synthesis of compound **2.80**

Pyrolysis of the *o*-anisidine derived compound **2.55** gave a single product as a pale yellow solid. The ¹H NMR spectrum was consistent with the structure and melting point of the compound was consistent with the literature data of 8-methoxyquinolinone **2.81**,³² isolated in 99% yield (Scheme **2.40**)



Scheme 2.40 Pyrolysis of compound **2.55**

This demonstrates that if the hydroxy-group is blocked as its ether, it behaves in the expected fashion and cyclisation occurs *meta* to the substituent to give the 8-substituted product.

Pyrolysis of the 2-acetoxy compound **2.56** gave a complex mixture of products by ^1H NMR spectroscopy, of which no identifiable peaks that could be assigned to any of the expected products were present.

Pyrolysis of the 2-aminothiophenol derived compound **2.57** gave an orange oil, different from the typical solids formed in this type of pyrolysis. After purification by column chromatography, an orange oil was isolated. The ^1H NMR spectrum of the compound featured a number of unusual features. There was no peak at $\delta_{\text{H}} = 6.2$ ppm, indicating that the product was not an 8-substituted quinolinone. There was also no peak at $\delta_{\text{H}} = 4.9$ ppm, showing that the product was not the 1,5-benzthioxazapinone. There was also a singlet at $\delta_{\text{H}} = 9.0$ ppm, highly deshielded and at higher chemical shift than is usually observed in quinolinones. The ^{13}C NMR spectrum showed the presence of 7 carbon atoms, instead of the 9 carbons expected, with the DEPT spectra showing the presence of 5 CH atoms and 2 quaternary carbons. The mass spectrum of the compound showed a molecular ion with m/z of 135. The product of the reaction was benzothiazole **2.82**, isolated in 48% yield (Figure 2.11, Scheme 2.42)

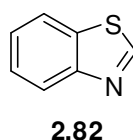
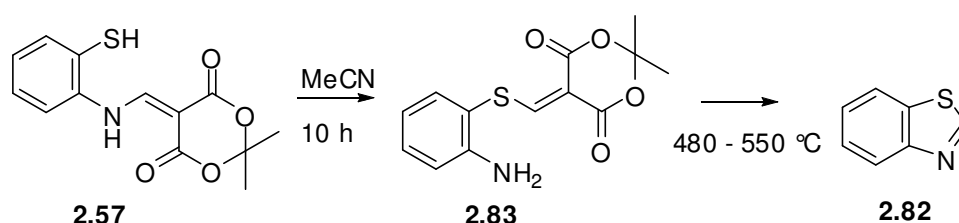


Figure 2.11 Structure of benzothiazole **2.82**

The ^1H , ^{13}C NMR data and boiling point of the compound were consistent with the

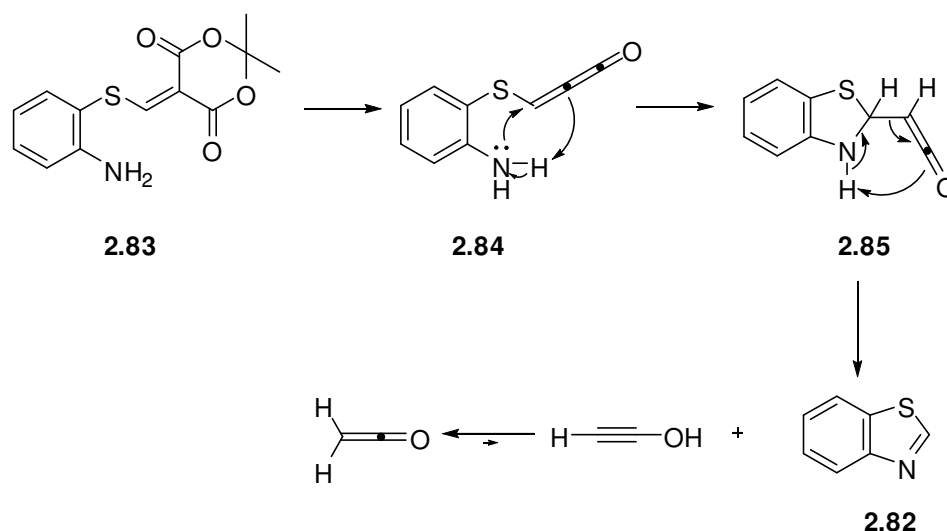
literature data of benzothiazole **2.82**.

Pommelet³³ previously reported the synthesis of benzothiazole by pyrolysis of an isomer of compound **2.83**. This analogue was synthesised by stirring compound **2.57** in acetonitrile for 10 hours (Scheme **2.41**).



Scheme 2.41 Synthesis of benzothiazole **2.82** from compound **2.83**

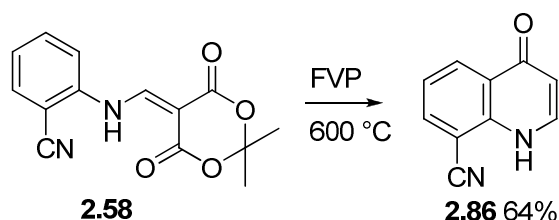
It is therefore likely that compound **2.57** underwent a rearrangement in the inlet to give compound **2.83**, which then underwent a similar reaction to give benzothiazole **2.82**. The mechanism proposed by Pommelet³³ involved attack of the methyleneketene **2.84** formed in the pyrolysis by the amino group to give the intermediate **2.85**. This can lose ketene, in the tautomeric form of ethynol, to give benzothiazole **2.82** (Scheme **2.42**)



Scheme 2.42 Mechanism for the formation of compound **2.82**

This mechanism is supported by the matrix isolation experiments,³³ which detected the presence of ketene in the pyrolysate by IR spectroscopy.

The cyano- group is often a very stable group at high temperatures and the pyrolysis of the 2-cyano- compound **2.58** gave 8-cyanoquinolinone **2.86** in 64% yield (Scheme 2.43)

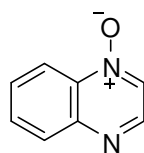


Scheme 2.43 Pyrolysis of compound **2.58**

In comparison, pyrolysis of the 2-nitro- compound **2.59** gave a yellow brown pyrolysate, with blue tinges in the pyrolysate. These blue tinges disappeared on warming of the pyrolysate and are typical of the formation of NO_x species. The ^1H NMR spectrum of the crude pyrolysate showed the presence of three products, with signs of the formation of a quinolinone-like product. The pyrolysate was subjected to column chromatography to separate the products.

The first isolated product showed the presence of four peaks in the ^1H NMR spectrum and was consistent with 2-nitroaniline, which was formed from the decomposition of the starting material in the inlet, isolated in 3% yield.

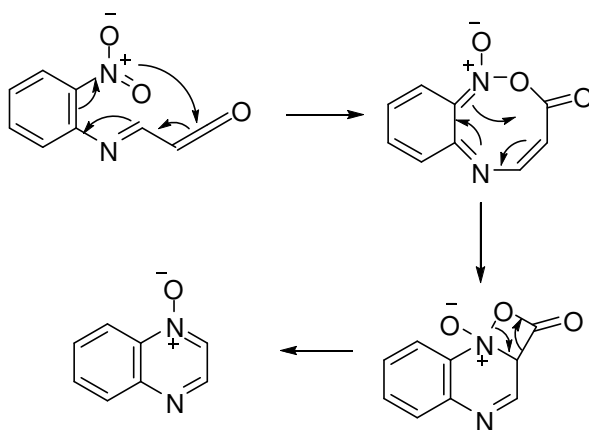
The second product showed the presence of six protons in the ^1H NMR spectrum. There were no typical quinolinone peaks in the spectrum, such as the doublet at $\delta_H = 6.2$ ppm. In addition two of the protons, at $\delta_H = 8.63$ and $\delta_H = 8.29$, showed small coupling constants of 3.5 Hz, which are typical of $J_{2,3}$ quinoline-type ring systems. The high chemical shifts of both protons indicate that they are both next to heteroatoms in the ring system. The product was identified by comparison with literature data³⁴ as quinoxaline-*N*-oxide **2.87**, isolated in 12% yield (Figure 2.12)



2.87

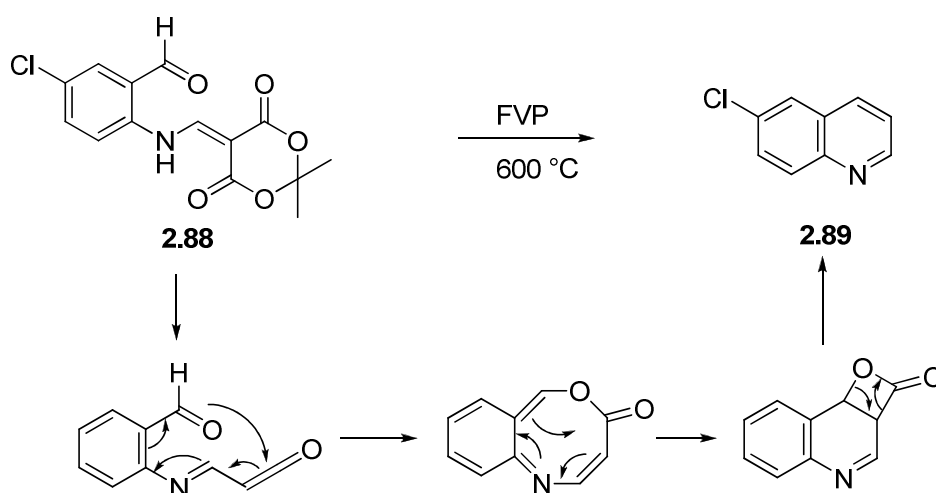
Figure 2.12 Structure of quinoxaline-*N*-oxide **2.87**

A possible mechanism for the formation of quinoxaline-*N*-oxide involves 8π electrocyclisation of the imidoyl ketene with the nitro group to give an eight membered ring. A second 6π electrocyclisation gives a tricyclic ring system, which then decarboxylates to give the product (Scheme 2.44).



Scheme 2.44 Mechanism for the formation of compound **2.87**

This type of electrocyclisation-decarboxylation mechanism has been observed previously. Pyrolysis of the 2-aminobenzaldehyde derived compound **2.88** leads to the formation of 6-chloroquinoline **2.89** (Scheme 2.45).²⁸



Scheme 2.45 Mechanism for the pyrolysis of compound **2.88**

The final product of the reaction was insoluble in most organic solvents, typical of a quinolinone product. The ^1H NMR spectrum of the compound showed the presence of six protons and was consistent with the parent quinolinone **2.90**, isolated in 35% yield (Figure **2.13**)

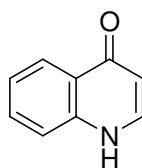
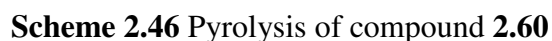



Figure 2.13 Structure of quinolin-4-one **2.90**

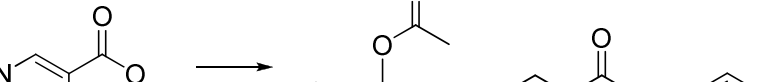
The formation of compound **2.90** proceeds via the standard electrocyclisation mechanism, but the loss of the nitro compound hints that the cyclisation may be occurring in the *ipso* position, with the loss of the nitro group by a radical mechanism, rather than loss of the nitro group from 8-nitroquinolinone.

Pyrolysis of the trifluoromethyl compound **2.60** gave an orange solid, isolated in 99% yield. The ^1H NMR spectrum and melting point of the compound were consistent with 8-trifluoromethylquinolinone **2.91** (Scheme **2.46**).³⁵





Scheme 2.47 Pyrolysis of compound **2.92**

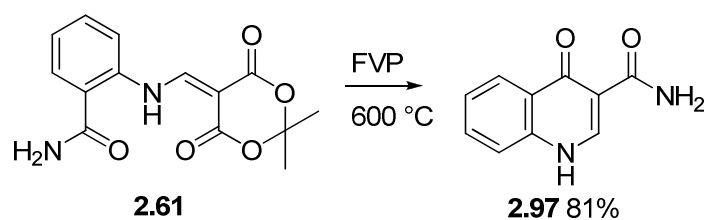


	2.95	2.90	2.96
550 °C	41	21	37
850 °C	95	5	0

Scheme 2.48 Pyrolysis of compound **2.93** at 550 °C and 850 °C

72

spectrum of the compound did not show the typical proton due to the 3-position of the molecule, as found for the pyrolysis of the chloro compound **2.51**. In addition the ^1H NMR spectrum showed the presence of two triplets and the presence of a four proton spin system was confirmed by a COSY experiment. The retention of the amide group was further demonstrated by the mass spectrum of the product, which showed the presence of a molecular ion at $m/z = 188$, consistent with the amide-substituted quinolinone. Based on this evidence, the product of the pyrolysis of compound **2.61** is therefore the 3-substituted product **2.97** (Scheme 2.49).



Scheme 2.49 Pyrolysis of compound **2.61**

Based on this result, the aptitude of migration of the amide group under FVP conditions must also be higher than that of hydrogen. One possible explanation might be due to hydrogen bonding between the NH of the amide and the carbonyl group, which serves to “anchor” and aid the migration of the amide to the 3-position of the product.

DFT calculations were employed to model the energy surfaces for the migrations of both the amide and hydrogen atom in this system. The calculations were performed at B3LYP/6-31G** level and the energy surface obtained is shown below (Figure 2.14)

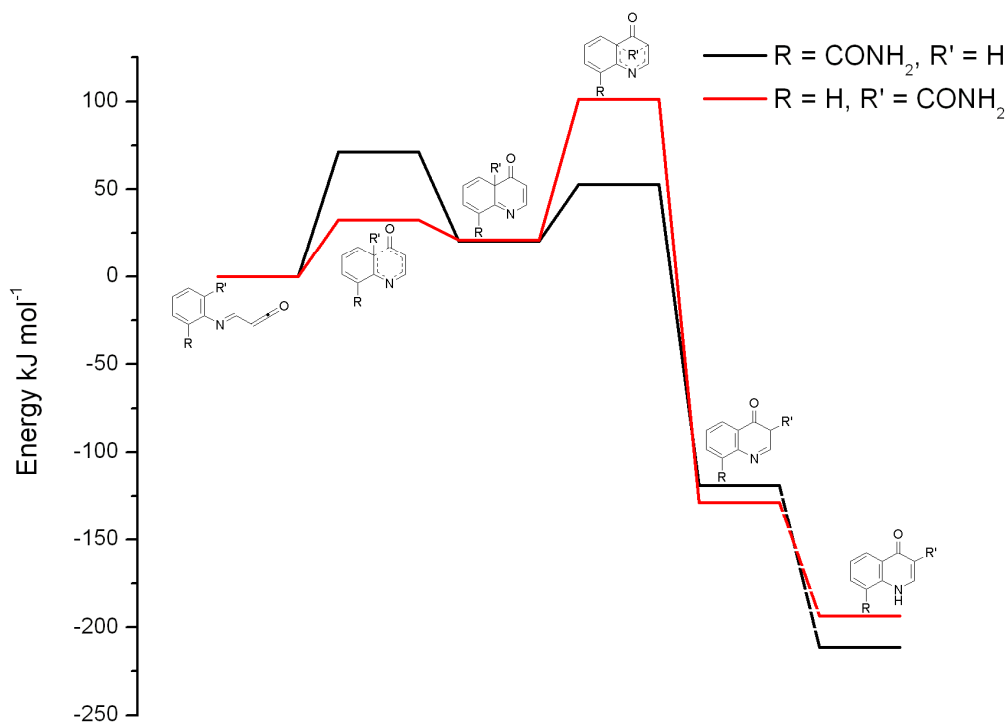


Figure 2.14 Energy surface for the formation of 3- and 8- carboxamidoquinolinones

From figure 2.14, it can be seen that the energy of the 1,5 sigmatropic shift for the amide is significantly lower than that for the hydrogen atom (25 vs 75 kJ mol⁻¹). From the transition state for the migration it can be seen that the hydrogen atom of the amide group is hydrogen bonding to the carbonyl group the quinolinone ring (Figure 2.15)

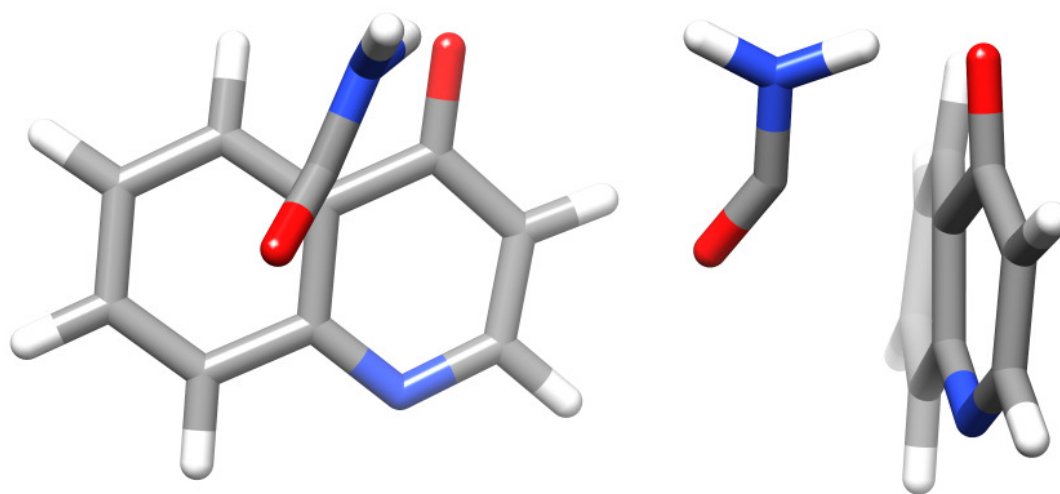
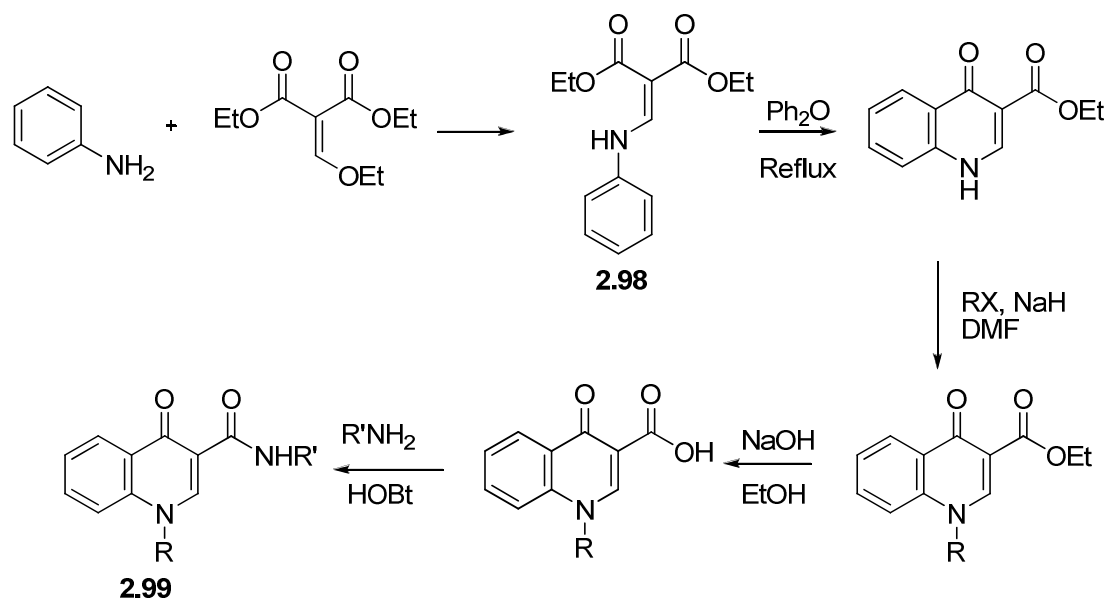


Figure 2.15 Structure of the transition for the 1,5 amide sigmatropic shift, showing the hydrogen bonding interaction

As previously stated, it is this interaction that aids the migration of the amide group in the sigmatropic shift to give the 3-substituted product.

Quinolinone-3-carboxamides have received interest in the literature as CB₂ cannabinoid receptor agonists.³⁶ A number of substituted amides were shown to have activity on the both CB₁ and CB₂ receptors, with the substituents such as aryls, benzyls and adamantyl. The route used to obtain these compounds involves the cyclisation of the diester acrylate **2.98**, followed by alkylation, saponification of the ester and formation of the amide **2.99** (Scheme 2.50)



Scheme 2.50 Representative synthesis of 3-carboxamidoquinolinones.

The pyrolysis route from the 2-aminobenzamide precursor allows for a potential three step route to this type of compound. However the functionality of the amide needs to be explored and its effect on the migration of the amide functionality. Six different substituted amides **2.100** – **2.105** were chosen, based on a number of factors (Figure 2.16)

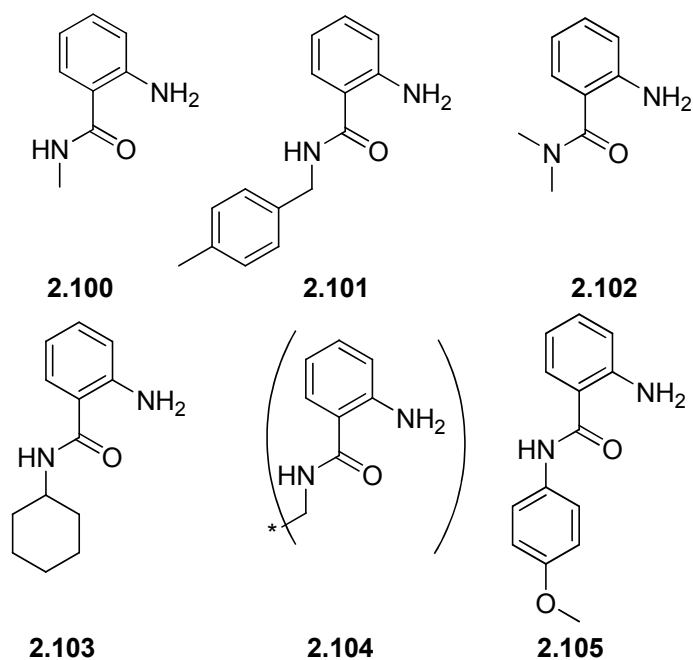
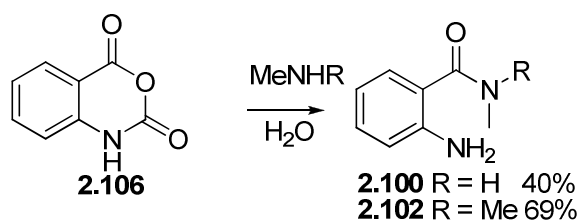


Figure 2.16 Amines chosen to explore the scope of the 1,5 amide sigmatropic shift

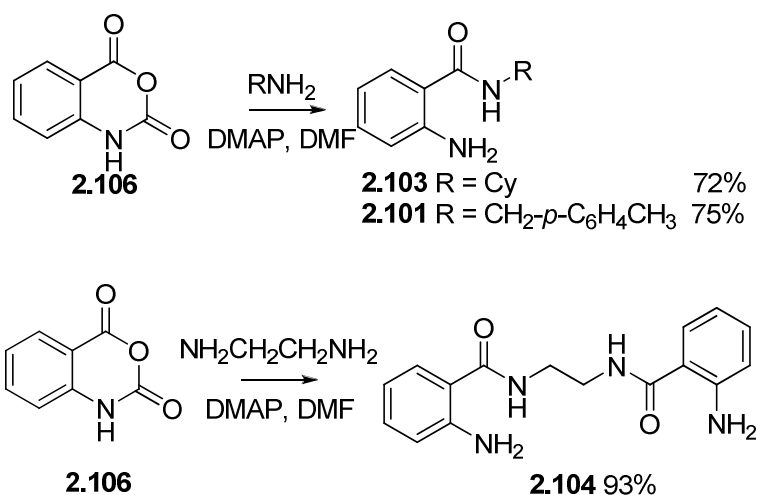
All of the chosen amides are known in the literature and easily synthesised from commercially available starting materials. The *N*-methyl amide **2.100** shows the effect of a simple alkyl substituent on the migration of the amide, while the benzyl amide **2.101** increases the steric bulk and is potentially synthetically useful as a protected amide. The dimethyl amide **2.102** shows the effect of the *N*-H on the migration of the amide, while the cyclohexyl amide **2.103** demonstrates the effect of steric bulk on the migration. The linked amide **2.104** may lead to the synthesis of a linked quinolinone and is interesting due to the effect of migrating amides on each other. Finally the aryl amide **2.105** shows the effect of the aromatic ring on the migration.

The *N*-methyl and *N*-dimethyl amides **2.100** and **2.102** were synthesised using a literature method,³⁷ which uses isatoic anhydride **2.106** and either methylamine or dimethylamine solutions in water, isolating the amides **2.100** and **2.102** in 40% and 69% yields (Scheme 2.51)



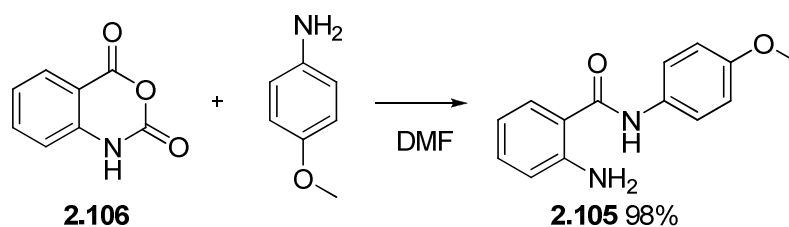
Scheme 2.51 Synthesis of compounds **2.100** and **2.102**

The *N*-cyclohexyl amide **2.103**, *N*-benzyl amide **2.101** and linked amide **2.104** were synthesised by addition of the appropriate amine to a solution of isatoic anhydride **2.106** in DMF (Scheme 2.52)



Scheme 2.52 Synthesis of compound **2.101**, **2.103** and **2.104**

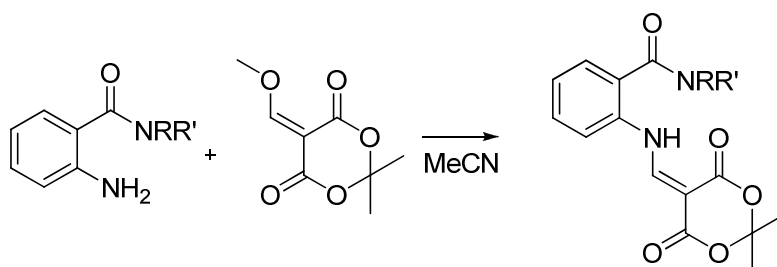
The *N*-aryl compound **2.105** was synthesised by heating a solution of isatoic anhydride **2.106** with *p*-anisidine in DMF in 98% yield after work-up (Scheme 2.53)



Scheme 2.53 Synthesis of compound **2.105**

With the six required amines in hand, the Meldrum's acid derivatives were made using the standard procedure. The yields and a general reaction scheme for these six

compounds are given below (Scheme 2.54 and Table 2.6)



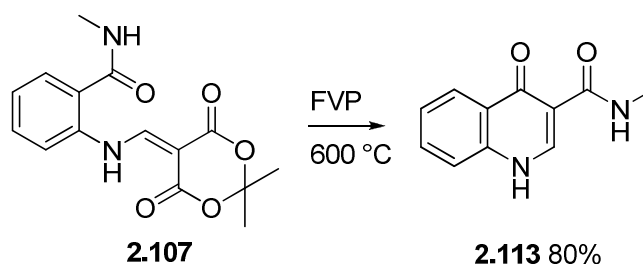
Scheme 2.54 General reaction scheme for the synthesis of compounds **2.107** – **2.112**

Compound No.	R	R'	Yield /%
2.107	CH ₃	H	99
2.108	CH ₂ - <i>p</i> -C ₆ H ₄ CH ₃	H	99
2.109	C ₆ H ₁₁	H	99
2.110	CH ₃	CH ₃	95
2.111	CH ₂ CH ₂ NHCO- <i>o</i> -C ₆ H ₄ NH ₂	H	90
2.112	<i>p</i> -C ₆ H ₄ OCH ₃	H	99

*Two equivalents of methoxymethylene Meldrum's acid used per equivalent of amine

Table 2.6 Yields for the synthesis of compounds **2.107** – **2.112**

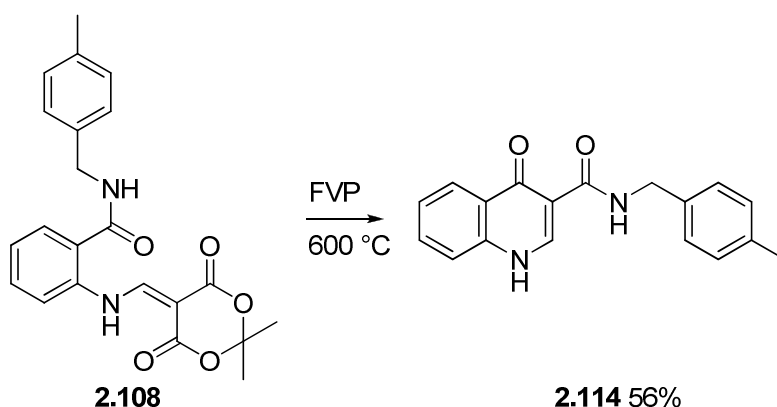
Pyrolysis of the *N*-methyl example **2.107** lead to the formation of a brown solid, with a molecular weight of $m/z = 202$. The ¹H NMR spectrum of the compound showed the presence of a singlet at $\delta_H = 8.05$ ppm, which is due to the 2-position of the quinolinone. The singlet shows that the 3-position is substituted, giving the structure of the product to be compound **2.113** in 80% yield (Scheme 2.55).



Scheme 2.55 Pyrolysis of compound **2.107**

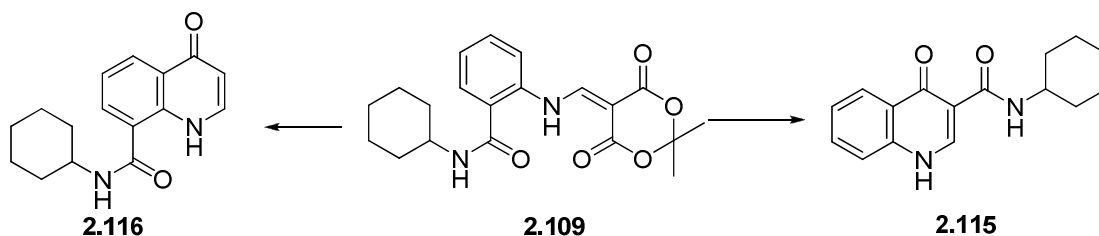
Pyrolysis of the benzyl compound **2.108** at 600 °C gave an orange solid, with a

molecular weight of $m/z = 292$, isolated in 56% yield. The ^1H NMR spectrum of the compound shows the presence of a benzyl group with peaks at $\delta_H = 5.16$ ppm and $\delta_H = 2.33$ ppm. The presence of a singlet at $\delta_H = 8.12$ ppm, as with the NHMe example above, shows that the amide is in the 3-position of the quinolinone and identifies the product as compound **2.114** (Scheme 2.56). Cleavage of the *N*-benzyl group, which can occur under FVP conditions,³⁸ was not observed due to the lower furnace temperature used.



Scheme 2.56 Pyrolysis of compound **2.108**

Pyrolysis of the cyclohexyl substituted compound **2.109** lead to the formation of a complex mixture of products from the ^1H NMR spectrum. However a quinolinone-like product could be identified from the crude spectrum and recrystallisation of the crude pyrostate from ethyl acetate gave an off-white solid with the expected molecular weight of 270. From this, the product could either be the 3 or 8-substituted quinolinones **2.115** and **2.116**, isolated in a 6% yield (Scheme 2.57)



Scheme 2.57 Potential products of the pyrolysis of compound **2.109**

From the ^1H NMR spectrum, the peak at $\delta_H = 7.84$ ppm, due to the proton in the 2-position of the quinolinone ring, shows coupling to another proton with a coupling

constant of 7.4 Hz, confirmed by a COSY spectrum (Figure 2.17).

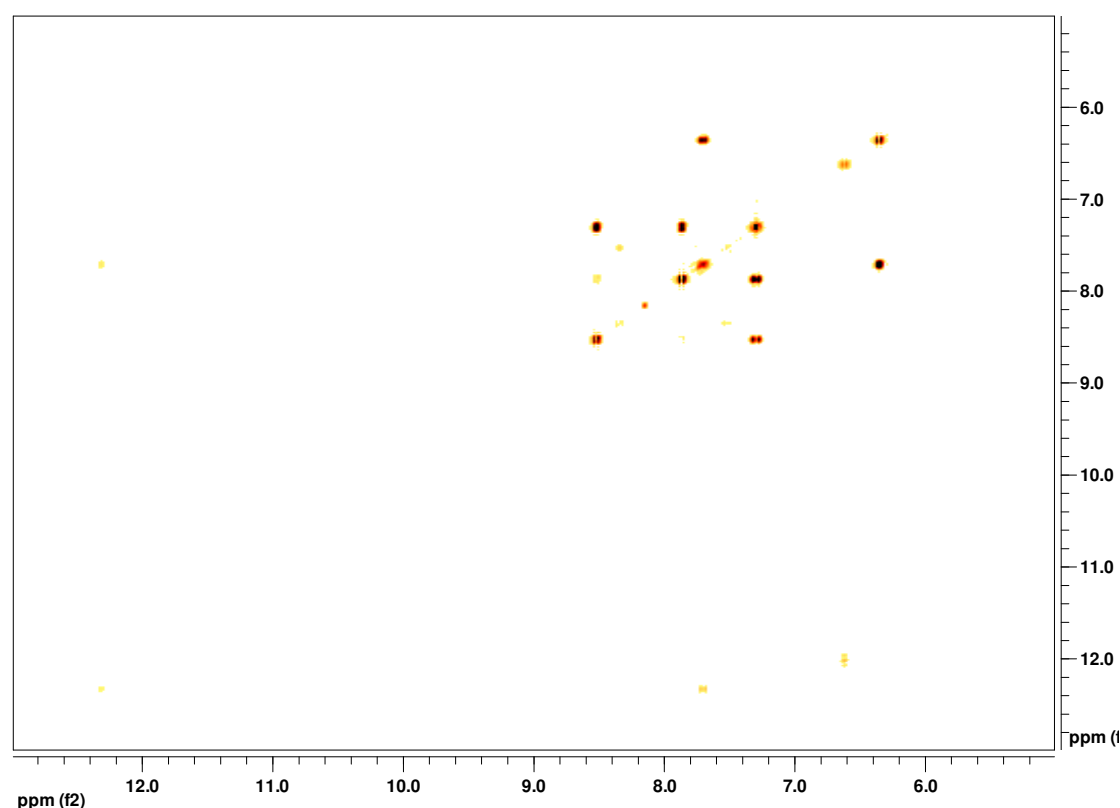
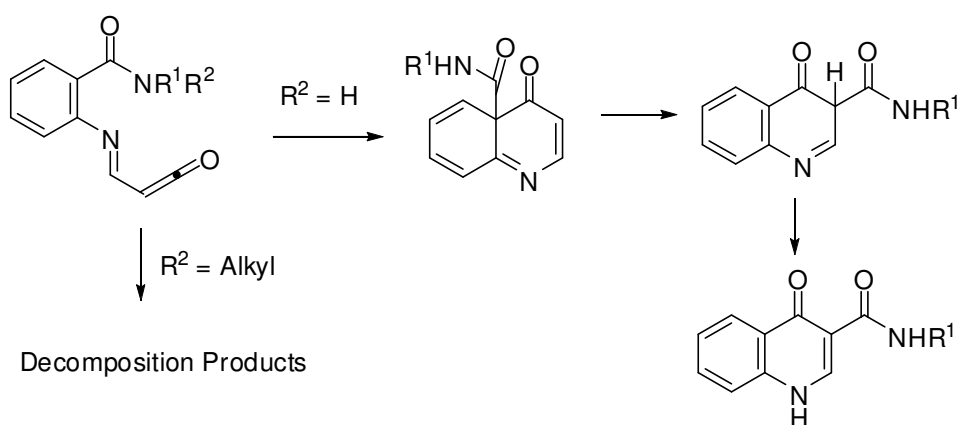


Figure 2.17 COSY spectrum of the product of the pyrolysis of compound **2.109**

No other correlations are observed for either proton, indicating that these are the protons in the 2 and 3-positions of the quinolinone ring system. The remaining aromatic protons show the presence of a 3-spin system, which indicates that the amide is in the 8-position (giving compound **2.116**) and has not undergone the 1,5 sigmatropic shift. This is probably due to the steric bulk of the cyclohexyl group, which has blocked the *ipso* cyclisation and forced the cyclisation to go *meta* to the amide group, leading to the formation of the 8-substituted product.

Pyrolysis of the dimethyl amide compound **2.110** led to the formation of a brown oil, the ^1H NMR spectrum of which showed a complex mixture of products. Neither the 3- or 8-substituted quinolinones could be identified from the spectrum. The implication of this result is that the nitrogen atom of the amide must have a free hydrogen atom and that it is this atom that facilitates the 1,5 sigmatropic shift of the amide to the 3-position of the quinolinone ring due to hydrogen bonding. Without this hydrogen atom, the reaction proceeds down other pathways, leading to complex

reaction mixtures (Scheme 2.58). However it is surprising that cyclisation *meta* to the substituent, to give the 8-substituted product, does not occur.



Scheme 2.58 Potential reactions of 2-carboxamido imidoalkenes

This reaction was modelled using DFT calculations to show that a free hydrogen atom was required on the amide to aid the 1,5 sigmatropic shift. The energy surface obtained is shown below (Figure 2.18)

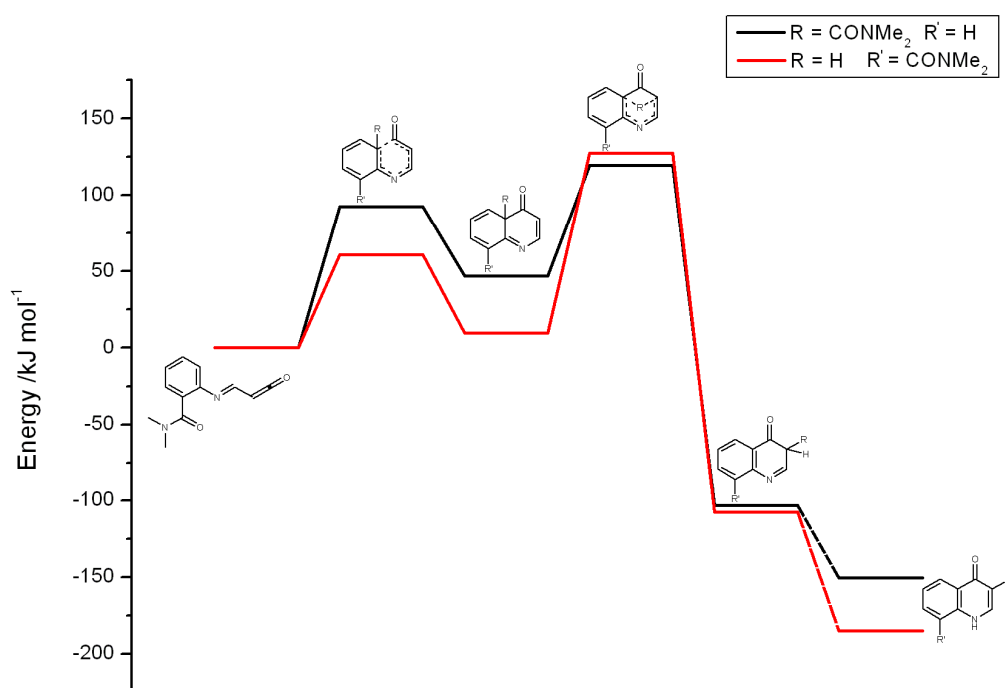
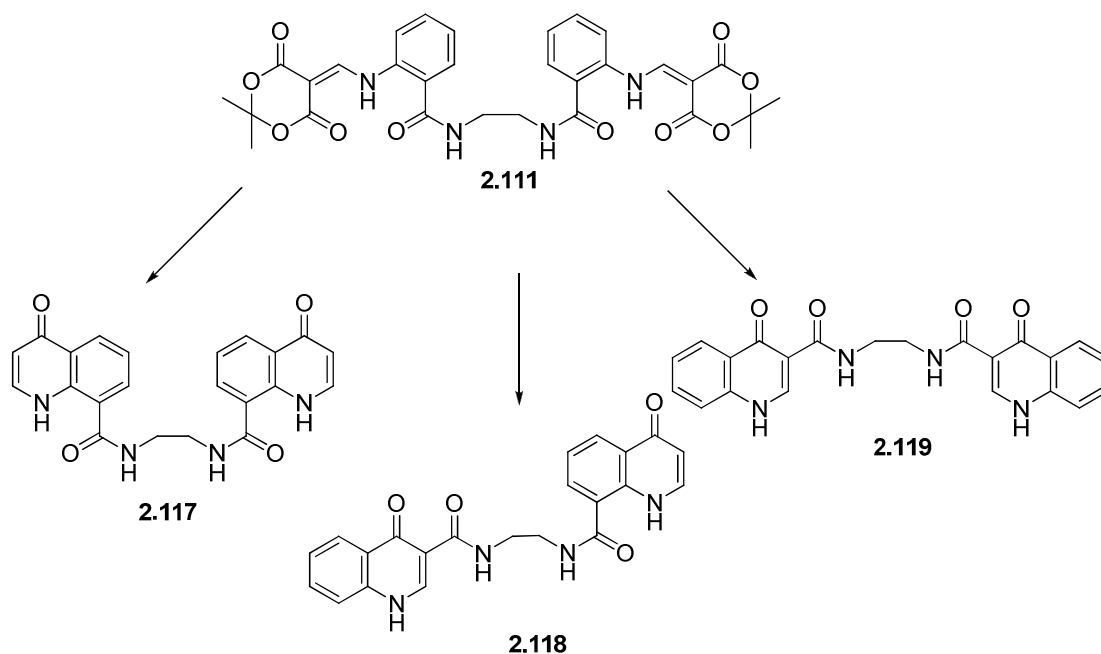


Figure 2.18 Energy surface for the formation of 3- and 8- *N,N*-dimethyl carboxamidoquinolinones

From figure **2.18**, the reason the 3-substituted product is not observed becomes apparent. The energy of the initial cyclisation is higher for the *ipso*-cyclisation than for the *meta* cyclisation, as was the case in figure **2.14**. However the 1,5 sigmatropic shifts are now comparable in energy, which means that there is no longer an overwhelming advantage in forming the 3-substituted product.

Pyrolysis of the linked precursor **2.111** gave a pale yellow solid, which showed a molecular ion under ESI conditions of $m/z = 403$, which gives a molecular weight of 402. With this example, three products **2.117** – **2.119** are possible based on the possible migrations of the linkage (Scheme **2.59**)



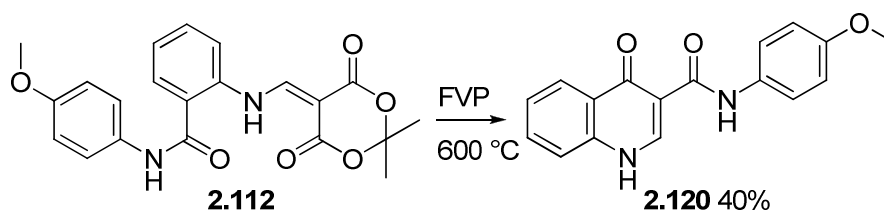
Scheme 2.59 Potential products of the pyrolysis of compound **2.111**

From the ^1H NMR spectrum, a singlet can be observed at $\delta_H = 8.60$ ppm due to the proton in the 2-position, which shows that the product obtained is the 3,3-linked product **2.119**. This shows that the migratory aptitudes of both amide groups are equal, giving rise to the observed product **2.119**.

Pyrolysis of the aryl amide compound **2.112** led to the formation of a brown solid, which was recrystallised from ethanol to give a pale brown solid, in 40% yield. The ESI mass spectrum of the compound showed the presence of a molecular ion at $m/z =$

295, consistent with a molecular weight at 294.

From the ^1H NMR spectrum of the compound, a singlet can be observed at $\delta_{\text{H}} = 8.12$ ppm which is typical for the proton in the 2-position of the molecule. Therefore the product from the reaction was identified as the 3-substituted product **2.120** (Scheme 2.60)

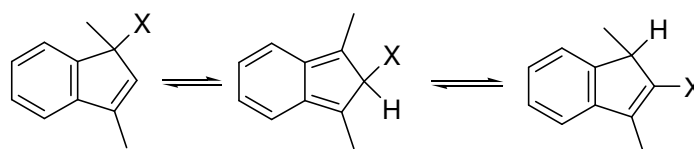


Scheme 2.60 Pyrolysis of compound **2.112**

The migration of amide groups under FVP groups has been demonstrated. A NH amide is required for the migration to be successful, with disubstituted amides giving no identifiable products (not even the 8-substituted product). The group on the amide can be varied with simple alkyl, benzyl and aryl substituents giving the 3-substituted products in moderate to good yields. With bulky groups (such as cyclohexyl), the 8-substituted product was obtained in reduced yield.

2.2.2.4 Migratory Aptitudes of Substituents in Sigmatropic Shifts

Migratory aptitudes of substituents are an important factor in sigmatropic shifts. However only one system has been studied in depth and is based on the 1,5 sigmatropic shifts in indenenes in solution phase (Scheme 2.61).³⁹



Scheme 2.61 Sigmatropic shifts of substituents in indenenes

For this system, the migratory aptitudes were found, in decreasing order, to be: $\text{HCO} > \text{Bz} \sim \text{Ac} > \text{H} > \text{Vinyl} > \text{CONHMe} > \text{CO}_2\text{Ph} > \text{CO}_2\text{Me} > \text{CN} \sim \text{Alkyne} > \text{Alkyl}$.

In quinolinone system, the following groups gave the 8-substituted quinolinone and therefore must have a lower migratory aptitude than hydrogen: H > MeO, Me, Et, CN, F, OH, CO₂Me, CF₃. The following groups gave the 3-substituted product and have a greater migratory aptitude than hydrogen: Cl, CONH₂, CONHR, COMe > H. This gives the overall order to be: Cl, CONH₂, CONHR, COMe > H > MeO, Me, Et, CN, F, OH, CO₂Me, CF₃.

In general, these results are in broad agreement with those of the indene system, with a few exceptions. The main exception is the amide groups, CONH₂ and CONHR. These can be explained as a special case in our system, due to the hydrogen bonding in the transition state of the sigmatropic shift. Solution phase pyrolysis of CONH₂ compound **2.61** also gave the 3-substituted product, which indicates that this hydrogen bonding interaction is strong enough to overcome any intermolecular mechanisms for the 1,5 hydrogen shift that may occur in solution phase. The other is the chlorine group, which has not been studied for the indene system.

2.3 Conclusion

The pyrolysis of *ortho*-aniline derived Meldrum's acid precursors has been explored. In general most substituents gave the 8-substituted quinolinones in good yields with a few exceptions. Chlorine and amide groups have been shown to undergo a 1,5 sigmatropic shift to give 3-substituted quinolinones as the major product. The hydroxy- group gave a mixture of two products, the expected 8-hydroxyquinolinone and 1,5-benzoxazepinone in roughly equal amounts. The thiol group was shown to undergo a different reaction to give benzothiazole. The nitro group gave 3-products: quinolinone, 3-nitroaniline and quinoxaline-*N*-oxide.

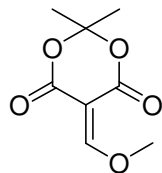
Some of the unexpected reactions were shown to only occur in the gas-phase, giving different products to solution phase pyrolyses. This allows flexibility, with the ability to obtain a different product by changing the pyrolysis method.

The migratory aptitudes of the system were also considered, with the order being similar to a previously studied system³⁹ with a few exceptions. However more work

is needed in this area for different structural features, as the work in the field is limited to a few examples, mainly based on an indene system.

Experimental

Methoxymethylene Meldrum's Acid **2.37**

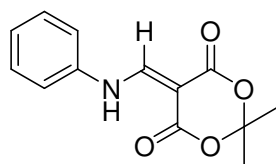


Meldrum's Acid (28.8 g, 120 mmol) and trimethyl orthoformate (140 cm³) were heated to reflux for 3 h. The mixture was cooled to room temperature, then placed in the freezer overnight. The yellow-orange precipitate was filtered off and washed with light petroleum to give methoxymethylene Meldrum's acid **2.37** as a pale yellow solid (14.7 g, 40%); mp 126 – 127 °C (lit.²⁸ 121 -122 °C).

General Method A – Reaction of Anilines with Methoxymethylene Meldrum's Acid **2.37**

A solution of the appropriately substituted aniline (1 equivalent) dissolved in the minimum amount of acetonitrile was added to a solution of methoxymethylene Meldrum's acid **2.37** (1 equivalent) dissolved in acetonitrile. The mixture was allowed to stand for 15 min and the solvent removed under vacuum to give the product.

2,2-Dimethyl-5-phenylaminomethylene-[1,3]dioxane-4,6-dione **2.31**



Using general method A, aniline (0.279 g, 3 mmol) gave 2,2-dimethyl-5-phenylaminomethylene-[1,3]dioxane-4,6-dione as a yellow solid (0.754 g, 99%); δ_H 11.24 (1H, d, 3J 14.4), 8.67 (1H, d, 3J 14.4), 7.49 – 7.42 (2H, m), 7.33 – 7.26 (3H, m) and 1.77 (6H, s).

2,2-Dimethyl-5-phenylaminomethylene-[1,3]dioxane-4,6-dione-*d*₅ **2.36**

Using general method A, aniline-*d*₇ (0.18 cm³, 2 mmol) gave the *d*₇-compound as a yellow solid, which was heated in methanol and allowed to cool to room temperature. Removal of the methanol gave 2,2-dimethyl-5-phenylaminomethylene-[1,3]dioxane-

4,6-dione- d_5 as a yellow solid (0.50 g, 99%); δ_H 11.24 (1H, d, 3J 14.4), 8.64 (1H, d, 3J 14.4) and 1.75 (6H, s).

Pyrolysis of Compounds **2.35** and **2.36** – Deuterium Experiments

The d_5 -precursor **2.36** was pyrolysed by the standard pyrolysis procedures.

N-Deuteriated compound **2.35** was synthesised prior to pyrolysis by heating compound **2.32** in methanol- d in a dried inlet tube. Removal of the methanol under high vacuum and subsequent pyrolysis gave the following results:

Pyrolysis of deuteriated compound **2.36** (T_f 500 °C) gave a yellow solid, which was dissolved in d_6 -DMSO. The percentage of incorporation of deuterium into the 3 position was measured to be 73% by 1H NMR spectroscopy (500 MHz).

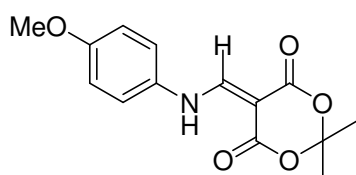
Pyrolysis of *N*-deuteriated compound **2.35** (T_f 500 °C) gave a yellow solid, which was dissolved in d_6 -DMSO. The percentage of incorporation of deuterium into the 3 position was measured to be 64% by 1H NMR spectroscopy (500 MHz).

Solution phase pyrolysis

Compound **2.36** (0.1 g) was added to a refluxing solution of Dowtherm A (1 cm³) and maintained at reflux for 20 min. The solution was allowed to cool and the precipitated using petroleum ether (25 cm³). The brown precipitate was dissolved in d_6 -DMSO and the 1H NMR spectrum recorded. This showed the percentage of incorporation of deuterium into the 3-position to be 35% by 1H NMR spectroscopy.

Synthesis of 6-Substituted Quinolin-4-ones

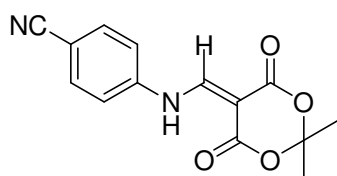
5-[(4-Methoxyphenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.42**



Using general method A, *p*-ansidine (1.23 g, 10 mmol) gave 5-[(4-methoxyphenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.42** as an off-yellow

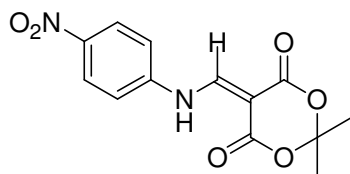
solid (2.738 g, 99%); mp 156 – 158 °C (from ethanol, lit.⁴⁰ 163 – 164 °C); δ_H 11.23 (1H, d, 3J 14.5), 8.52 (1H, d, 3J 14.5), 7.18 (2H, d, 3J 9.1), 6.94 (2H, d, 3J 9.1), 3.82 (3H, s) and 1.74 (6H, s).

5-[(4-Cyanophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.43**



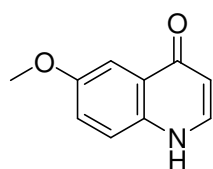
Using general method A, *p*-aminobenzonitrile (0.236 g, 2 mmol) gave 5-[(4-cyanophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.43** as an off-yellow solid (0.492 g, 85%); mp 223 – 224 °C (from ethanol); δ_H 11.32 (1H, d, br, 3J 14.0), 8.67 (1H, d, 3J 14.0), 7.76 (2H, d, 3J 8.4), 7.36 (2H, d, 3J 8.8) and 1.76 (6H, s).

5-[(4-Nitrophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.44**



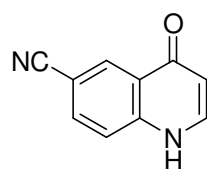
Using the general method A, *p*-nitroaniline (1.38 g, 10 mmol) gave 5-[(4-nitrophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.44** as a yellow solid (2.816 g, 96%); mp 223 - 226 °C (lit.⁴⁰ 215 – 217 °C); δ_H 11.40 (1H, d, br, 3J 14.5), 8.70 (1H, d, 3J 14.5), 8.29 (2H, d, 3J 8.7), 7.86 (2H, d, 3J 8.7) and 1.71 (6H, s).

6-Methoxyquinolin-4-one **2.45**

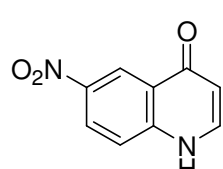


Pyrolysis of 5-[(4-methoxyphenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.42** (0.60 g, T_f 600 °C, T_i 170 °C, t 50 min, P $1.6 - 1.7 \times 10^{-2}$ Torr) gave a yellow solid (0.403 g, quant.), recrystallised from methanol to give 6-methoxyquinolin-4-one **2.45** as a pale yellow solid (0.24 g, 61%); mp 243 – 246 °C (from methanol) (lit.,⁴⁰ 245-246 °C); δ_H (360 MHz) 11.78 (1H, s, br), 7.87 (1H, d, 3J 7.2), 7.53 (1H, d, 3J 5.5), 7.52 (1H, s), 7.30 (1H, dd, 3J 9.1, 4J 2.1), 6.03 (1H, d, 3J 7.2) and 3.85 (3H, s).

6-Cyanoquinolin-4-one **2.46**

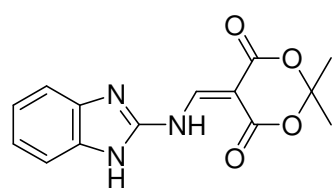
 Pyrolysis of 5-[(4-cyanophenylamino)methylene]-2,2-dimethyl [1,3]dioxane-4,6-dione **2.43** (w 0.610 g, T_f 600 °C, T_i 200 °C, t 1.25 h, P $2.2 - 2.4 \times 10^{-2}$ Torr) gave 6-cyanoquinolin-4-one **2.46** as an orange solid (0.358 g, 94%); mp 186 °C (from methanol); δ_H 8.47 (1H, dd, 3J 2.0, 4J 0.5), 8.06 (1H, d, 3J 7.7), 8.02 (1H, dd, 3J 8.7, 4J 1.8), 7.72 (1H, dd, 3J 8.7, 4J 0.5) and 6.20 (1H, d, 3J 7.7).

6-Nitroquinolin-4-one **2.47**

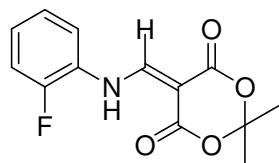
 Pyrolysis of 5-[(4-nitrophenylamino)methylene]-2,2-dimethyl [1,3]dioxane-4,6-dione **2.44** (w 0.664 g, T_f 600 °C, T_i 200 °C, t 1h, P $2.1 - 2.6 \times 10^{-2}$ Torr) gave 6-nitroquinolin-4-one **2.47** as a yellow solid (0.283 g, 66%); mp >320 °C (from methanol, lit.,⁴⁰ 337 – 342 °C); δ_H (250 MHz) 8.88 (1H, d, 4J 2.8), 8.46 (1H, dd, 3J 9.2, 4J 2.8), 8.09 (1H, d, 3J 8.3), 7.76 (1H, d, 3J 9.2) and 6.24 (1H, d, 3J 8.3).

Synthesis of 8-Substituted Quinolin-4-ones

5-[(1*H*-Benzimidazol-2-ylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.48**

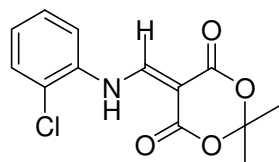
 Using general method A, 2-aminobenzimidazole (0.133 g, 1 mmol) gave 5-[(1*H*-benzoimidazol-2-ylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.48** as a yellow solid (0.286 g, 99%) mp >310 °C; δ_H 9.20 (1H, s), 7.73 – 7.68 (2H, m), 7.45 – 7.35 (2H, m) and 1.89 (6H, s); δ_C 163.22 (quat), 151.36, 147.46 (quat), 137.32 (quat), 137.22 (quat), 122.41, 121.47, 114.92 (2CH), 111.75 (quat), 104.93 (quat), 89.86 (quat), 26.98 (2CH₃).

5-[(2-Fluorophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.50**



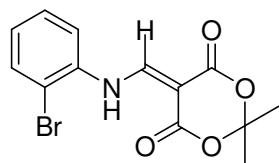
Using the general method A, 2-fluoroaniline (0.278 g, 2.5 mmol) gave 5-[(2-fluorophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.50** as a yellow solid (0.627 g, 95%); mp 182 – 185 °C (from ethanol); (Found C, 59.0; H, 4.2; N, 5.35; C₁₃H₁₂FNO₄ requires C, 58.85; H, 4.5; N, 5.3.) δ_H 11.41 (1H, d, 3J 14.3), 8.73 (1H, d, 3J 14.3), 7.46 – 7.26 (4H, m) and 1.92 (6H, s); δ_C 165.42 (quat), 163.28 (quat), 162.89 (quat), 158.96 (quat), 152.84, 133.99 (quat), 119.84, 119.71, 117.09, 116.72, 105.10 (quat), 87.19 (quat) and 26.89 (2CH₃); m/z 265 (M⁺, 30%), 207 (100), 162 (94), 135 (75) and 108 (14).

5-[(2-Chlorophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.51**



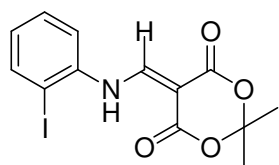
Using general method A, 2-chloroaniline (0.318 g, 2.5 mmol) gave 5-[(2-chlorophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.51** as a yellow solid (0.709 g, quant.); mp 120 – 122 °C (from ethanol, lit.⁴¹ 126 – 127 °C); δ_H 11.67 (1H, d, br, 3J 13.5), 8.66 (1H, d, 3J 13.5), 7.48 (1H, dd, 3J 7.9, 4J 1.4); 7.45 – 7.32 (2H, m), 7.21 (1H, dd, 3J 7.1, 4J 2.2) and 1.76 (6H, s); δ_C 164.97 (quat), 163.16 (quat), 151.45, 134.83 (quat), 130.32, 128.13, 126.87, 124.44, 116.49, 105.10 (quat), 88.50 (quat) and 20.91 (2CH₃).

5-[(2-Bromophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.52**



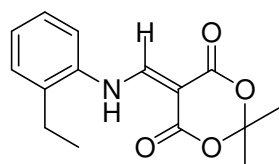
Using general method A, 2-bromoaniline (1.72 g, 10 mmol) gave 5-[(2-bromophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.52** as an off-yellow solid (3.26 g, quant.); mp 157 – 159 °C (from ethanol, lit.³¹ 157 – 158 °C); δ_H 11.66 (1H, d, 3J 14.0), 8.66 (1H, d, 3J 14.0), 7.65 (1H, dd, 3J 8.3, 4J 0.4), 7.43 – 7.38 (2H, m), 7.14 (1H, m) and 1.94 (6H, s); δ_C 165.00 (quat), 163.28 (quat), 151.71, 136.25 (quat), 133.62, 128.87, 127.32, 116.79, 114.42 (quat), 105.18 (quat), 88.52 (quat) and 27.00 (2CH₃).

5-[(2-Iodophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.53**



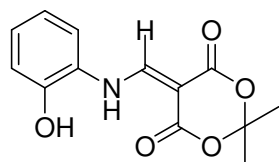
Using general method A, 2-iodoaniline (0.548 g, 2.5 mmol) gave 5-[(2-iodophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.53** as an off-yellow solid (0.933 g, quant.); mp 176 – 178 °C (from ethanol); (Found C, 42.0; H, 3.1; N, 3.65; C₁₃H₁₂INO₄ requires C, 41.8; H, 3.2; N 3.75.) δ_H 11.50 (1H, br, d, 3J 13.5), 8.60 (1H, d, 3J 13.5), 7.90 (1H, dd, 3J 7.9, 4J 1.2), 7.45 (1H, ddd, 3J 8.4, 4J 1.5, 5J 0.9), 7.34 (1H, dd, 3J 8.2, 4J 1.6), 7.00 (1H, ddd, 3J 8.8, 4J 7.2, 5J 1.6) and 1.77 (6H, s); δ_C 164.95 (quat), 163.27 (quat), 152.26, 140.13, 139.28 (quat), 129.72, 127.78, 117.08, 105.13 (quat), 89.40 (quat), 88.27 (quat) and 26.98 (2CH₃); m/z 373 (M⁺, 3%), 344 (6), 315 (8), 218 (100) and 92 (25).

5-[(2-Ethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.49**



Using general method A, 2-ethylaniline (0.605 g, 5 mmol) gave 5-[(2-ethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.49** as a yellow solid (1.361 g, 99%); mp 95 -97 °C (from ethanol) (Found C., 65.45; H., 6.05; N., 5.1. C₁₅H₁₇NO₄ requires C., 65.45; H., 6.2; N., 5.1%); δ_H 11.46 (1H, d, 3J 14.1), 8.56 (1H, d, 3J 14.1), 7.23 – 7.14 (4H, m), 2.67 (2H, q, 3J 7.6), 1.68 (6H, s) and 1.18 (3H, t, 3J 7.6); δ_C 165.77 (quat), 163.44 (quat), 153.68, 135.83 (quat), 134.13 (quat), 129.63, 127.49, 126.97, 116.79, 105.02 (quat), 87.13 (quat), 26.90 (2CH₃), 24.08 (CH₂) and 13.76 (CH₃); m/z 275 (M⁺, 38%), 217 (100), 172 (25), 144 (56), 130 (44) and 106 (48).

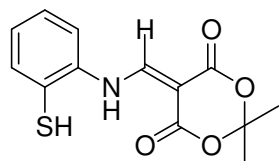
5-[(2-Hydroxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.54**



Using general method A, 2-aminophenol (1.09 g, 10 mmol) gave 5-[(2-hydroxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.54** as a off-yellow solid (2.42 g, 92%); mp 206 – 208 °C (from ethanol, lit.,³⁹ 213 – 214 °C); δ_H (*d*₆-DMSO) 11.47 (1H, d, 3J 14.7), 10.63 (1H, s), 8.72 (1H, d, 3J 14.7), 7.65 (1H, dd, 3J 8.1, 4J 1.4), 7.09 (1H, m), 6.97 (1H, dd, 3J 8.1, 4J 1.4), 6.89 (1H, dd, 3J 8.1, 4J 1.4)

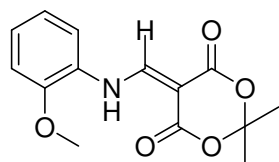
and 1.67 (6H, s); δ_C (d_6 -DMSO) 164.62 (quat), 162.49 (quat), 151.29, 147.00 (quat), 126.66, 125.64 (quat), 119.88, 116.25, 115.71, 104.17 (quat), 86.30 (quat) and 26.35 (2CH₃); m/z 263 (M⁺, 16%), 205 (100), 161 (31), 133 (43) and 120 (37).

5-[(2-Mercaptophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.57**



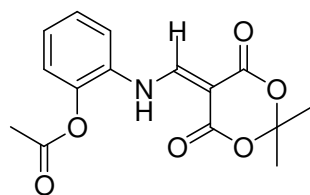
Using general method A, 2-aminothiophenol (0.625 g, 5 mmol) gave 5-[(2-mercaptophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.57** as a yellow solid (1.257 g, 90%); mp 147 - 149 °C (lit.⁴² 150 – 152 °C); δ_H 11.90 (1H, br, d, 3J 14.1), 8.77 (1H, d, 3J 14.1), 7.68 (2H, m), 7.50 (1H, d, 3J 4.7), 7.21 (1H, m) and 1.88 (6H, s); δ_C 165.14 (quat), 163.53 (quat), 151.83, 138.63 (quat), 136.37, 129.33, 126.60, 119.60 (quat), 116.53, 105.11 (quat), 88.17 (quat) and 27.53 (2CH₃); m/z 279 (M⁺, 3%), 221 (99), 175 (84) and 136 (100).

5-[(2-Methoxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.55**



Using the general procedure, *o*-anisidine (0.308 g, 2.5 mmol) gave 5-[(2-methoxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.55** as a yellow solid (0.722 g, quant.); mp 151 – 153 °C (from ethanol, lit.³¹ 150 – 151 °C); δ_H 11.76 (1H, d, 3J 14.7), 8.88 (1H, d, 3J 14.7), 7.56 (1H, dd, 3J 7.9, 4J 1.1), 7.44 (1H, td, 3J 7.9, 4J 1.5), 7.27 – 7.19 (2H, m), 4.10 (3H, s) and 1.97 (6H, s).

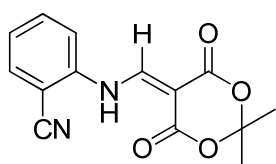
5-[(2-Acetoxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.56**



Triethylamine (0.66 cm³) was added to a solution of 5-[(2-hydroxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.54** (0.789 g, 3 mmol) in DCM (25 cm³) and the resulting solution cooled to 0 °C. Acetyl chloride (0.5 cm³) was added and the mixture stirred for 2 h at room temperature. The mixture was washed with NaHCO₃ (sat), brine (sat), the organic extract dried over MgSO₄ and the

solvent removed to give 5-[(2-acetoxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.56** as a yellow solid (0.9169 g, quant.); mp 141 – 143 °C (from ethanol); (Found M^+ 305.08916, $C_{15}H_{15}NO_6$ requires 305.08939); δ_H 11.53 (1H, d, br, 3J 14.2), 8.58 (1H, d, 3J 14.2), 7.38 – 7.16 (4H, m), 2.64 (3H, s) and 1.60 (6H, s); δ_C 168.37 (quat), 165.57 (quat), 163.10 (quat), 151.45, 140.56 (quat), 129.91 (quat), 127.03, 126.63, 123.51, 115.78, 105.21 (quat), 88.02, 26.94 (2CH₃) and 20.66 (CH₃); m/z 305 (M^+ , 25%), 247 (50), 205 (100), 161 (23), 133 (49) and 109 (66).

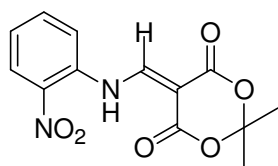
5-[(2-Cyanophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.58**



Using general method A, 2-aminobenzonitrile (1.18 g, 10 mmol) gave 5-[(2-cyanophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.58** (2.69 g, 99%); mp 153 – 154 °C (from ethanol) (Found C, 62.0; H, 4.55; N, 10.54.

$C_{14}H_{12}N_2O_4$ requires C, 61.75; H, 4.4; N, 10.3). δ_H 11.78 (1H, d, 3J 13.4), 8.72 (1H, d, 3J 13.4), 7.74 – 7.69 (2H, m), 7.52 (1H, d, 3J 8.3), 7.38 (1H, t, 3J 7.4) and 1.77 (6H, s); δ_C 164.90 (quat), 162.81 (quat), 151.82, 140.51 (quat), 134.50, 133.49, 126.22, 116.59, 114.92 (quat), 105.48 (quat) 103.69 (quat), 89.87 (quat) and 27.05 (2CH₃). m/z 272 (M^+ , 10%), 214 (86), 170 (100), 168 (100), 142 (72) and 102 (46).

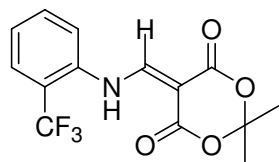
5-[(2-Nitrophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.59**



Using general method A, 2-nitroaniline (1.38 g, 10 mmol) gave 5-[(2-nitrophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.59** as a off-yellow solid (2.77 g, 95%); mp 181 - 182 °C (from ethanol, lit. 185 – 186 °C); δ_H (d_6 -DMSO) 8.56

(1H, d, 3J 13.7), 8.04 (1H, dd, 3J 7.1, 4J 1.0), 7.87 (1H, d, 3J 8.3), 7.64 (1H, t, 3J 7.3), 7.25 (1H, t, 3J 7.4) and 1.49 (6H, s); δ_C (d_6 -DMSO) 164.22 (quat), 162.63 (quat), 153.40, 138.33 (quat), 136.57, 134.23 (quat), 126.49, 126.37, 120.02, 105.03 (quat), 90.26 (quat) and 26.93 (2CH₃).

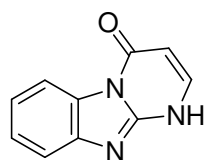
5-[(2-Trifluoromethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.60**



Using general method A, 2-trifluoromethylaniline (0.805 g, 5 mmol) gave 5-[(2-trifluoromethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.60** as a off-yellow solid (1.552 g, 99%); mp 124 – 127 °C (from ethanol); (Found C, 53.15; H, 3.5; N, 4.45. $C_{14}H_{12}F_3NO_4$ requires C, 53.35; H, 3.8; N, 4.45%); δ_H 11.82 (1H, d, 3J 13.9), 8.62 (1H, d, 3J 13.9), 7.75 – 7.65 (2H, m), 7.49 (1H, d, 3J 8.1), 7.45 (1H, t, 3J 6.7) and 1.79 (6H, s); δ_C 165.62 (quat), 163.69 (quat), 154.04, 136.64 (quat), 134.20, 127.69, 127.02, 121.71 (quat, 2J 24.7), 119.76, 105.85 (quat), 89.72 (quat) and 27.57 (2CH₃) one quat. not apparent; m/z 315 (M^+ , 15%), 257 (100), 229 (52), 212 (57), 165 (35) and 145 (31).

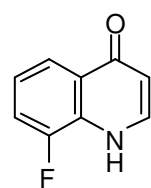
Synthesis of 8-Substituted Quinolin-4-ones.

1H-Benz[4,5]imidazo[1,2-*a*]pyrimidin-4-one **2.62**



Pyrolysis of compound **2.48** (w 0.323 g, T_f 600 °C, T_i 200 °C, P 2.3 – 2.6×10^{-2} Torr, t 1 h) gave a yellow solid (0.182 g) and recrystallisation from methanol to give 1H-benz[4,5]imidazo[1,2-*a*]pyrimidin-4-one **2.62** as a pale yellow solid (0.129 g, 62%); mp 285 – 287 °C (from methanol, lit.,⁴³ 290 °C); δ_H (d_6 -DMSO) 8.45 (1H, d, 3J 8.0), 8.00 (1H, d, 3J 7.1), 7.58 (1H, d, 3J 8.0), 7.50 (1H, td, 3J 7.1, 4J 1.2), 7.34 (1H, td, 3J 8.0, 4J 1.2) and 5.99 (1H, d, 3J 6.9); δ_C (d_6 -DMSO) 159.36 (quat), 148.99 (CH), 148.73 (quat), 134.47 (quat), 126.58 (quat), 125.58 (CH), 121.28 (CH), 115.25 (CH), 113.23 (CH) and 99.86.

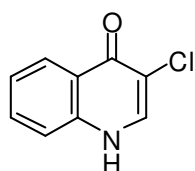
8-Fluoroquinolin-4-one **2.66**



Pyrolysis of 5-[(2-fluorophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.50** (w 0.308 g, T_f 600 °C, T_i 160 °C, P 2.1 – 2.6×10^{-2} Torr, t 30 min) gave 8-fluoroquinolin-4-one **2.66** as a pale yellow solid (0.193 g, quant.); mp 218 – 220 °C (from ethanol); δ_H 11.93 (1H, s, br),

7.97 (1H, d, 3J 7.4), 7.77 (1H, dd, 3J 9.4, 4J 2.8), 7.70 – 7.56 (2H, m) and 6.09 (1H, d, 3J 7.4). Compound previously reported by Madrid *et al.*¹⁹

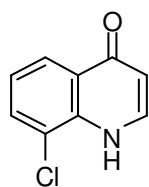
3-Chloroquinolin-4-one **2.67**



Pyrolysis of 5-[(2-chlorophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.51** (w 0.5164 g, T_f 600 °C, T_i 200 °C, P 2.2 – 2.5×10^{-2} Torr, t 23 min.) gave a yellow-brown solid.

Recrystallisation from methanol gave 3-chloroquinolin-4-one **2.67** as a pale brown solid (0.0988 g, 30%); mp 255 – 257 °C; δ_H (360 MHz, d_6 -DMSO) 12.31 (1H, s, br), 8.42 (1H, d, 3J 6.1), 8.17 (1H, dd, 3J 7.9, 4J 1.4), 7.70 (1H, ddd, 3J 8.6, 4J 7.2, 5J 1.4), 7.62 (1H, d, 3J 8.3) and 7.40 (1H, ddd, 3J 8.3, 4J 6.8, 5J 1.1); δ_C (90 MHz, d_6 -DMSO) 171.28 (quat), 139.23 (quat), 138.06, 132.02, 125.23, 124.78 (quat), 123.96, 118.66 and 114.18 (quat). NMR data matches literature data.⁴⁴

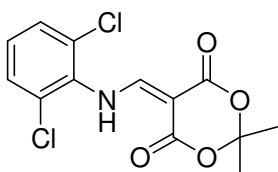
8-Chloroquinolin-4-one **2.68**



5-[(2-Chlorophenylamino)methylene]-2,2-dimethyl[1,3]dioxane-4,6-dione **2.51** (0.220 g) was added to a refluxing solution of Dowtherm A (2 cm³) and maintained at reflux for 20 min. The solution was allowed to cool and the product precipitated using petroleum ether (25 cm³).

Collection by filtration gave 8-chloroquinolin-4-one **2.68** as a brown solid (0.099 g 71%); δ_H (d_6 -DMSO) 11.45 (1H, br, s), 8.13 (1H, dd, 3J 8.3, 4J 1.3), 7.96 – 7.85 (2H, m), 7.37 (1H, t, 3J 8.0) and 6.18 (1H, d, 3J 7.5); δ_C (d_6 -DMSO) 176.65 (quat), 140.28, 136.76 (quat), 131.94, 127.35 (quat), 124.59, 123.57, 121.77 (quat) and 109.78. NMR data matches literature spectrum.⁴⁵

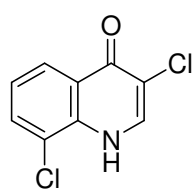
5-[(2,6-Dichloro-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.69**



Using general method A, 2,6-dichloroaniline (1.62 g, 10 mmol) gave 5-[(2,6-dichloro-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.69** as a yellow solid (2.89 g,

91%); mp 119 – 120 °C (from ethanol); (Found C, 49.6; H, 3.15; N, 4.3; C₁₃H₁₁Cl₂NO₄ requires C, 49.4; H, 3.5; N, 4.45); δ_H 11.05 (1H, d, 3J 13.9), 8.55 (1H, d, 3J 13.9), 7.45 (2H, d, 3J 7.9), 7.08 (1H, dd, 3J 7.7, 4J 1.0) and 1.79 (6H, s); δ_C 165.23 (quat), 162.88 (quat), 158.18, 133.20 (quat), 129.53 (2 quat), 129.25 (2CH), 128.49, 105.17 (quat), 88.02 (quat) and 27.03 (2CH₃); m/z 317 (M⁺, 11%), 315 (M⁺, 16), 259 (59), 257 (89), 180 (42) and 178 (100).

3,8-Dichloroquinolin-4-one **2.70**



Pyrolysis of 5-[(2,6-dichloro-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.69** (w 0.354 g, T_f 600 °C, T_i 190 °C, P 2.5 – 3.0×10^{-2} Torr, t 15 min) gave a yellow-brown solid. Minor soluble impurities were removed by distillation of DCM through the U-tube.

Suspension of the residual solid in acetone and removal of the solvent gave 3,8-dichloroquinolin-4-one **2.70** as a brown solid (0.128 g, 54%); mp 255 – 257 °C (decomp.); (Found M⁺ 212.97454, C₉H₅Cl₂NO requires 212.97427); δ_H (d_6 -DMSO) 11.94 (1H, br, s), 8.25 (1H, br, m), 8.18 (1H, dd, 3J 8.3, 4J 1.4), 7.93 (1H, dd, 3J 7.8, 4J 1.6) and 7.44 (1H, dd, 3J 8.3, 4J 7.7); δ_C (d_6 -DMSO) 170.86 (quat), 138.29, 135.69 (quat), 132.10, 125.94 (quat), 124.64, 124.67, 121.89 (quat) and 115.19 (quat); m/z 215 (M⁺, 35%), 213 (M⁺, 53), 163 (85), 161 (100) and 84 (85).

Pyrolysis of 5-[(2-bromo-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.52**

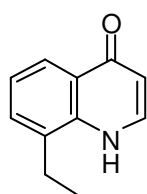
Pyrolysis of 5-[(2-bromo-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.52** gave a brown oil, the ¹H NMR spectrum of which did not indicate the presence of either the 3- or 8- substituted bromoquinolinones and no identifiable products could be detected.

Pyrolysis of 5-[(2-iodo-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.53**

Pyrolysis of 5-[(2-iodo-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-

dione **2.53** gave a black oil, the ^1H NMR spectrum of which did not indicate the presence of either the 3- or 8- substituted iodoquinolinones and no identifiable products could be detected. The DMSO solution did give a positive starch test, indicating the presence of molecular iodine.

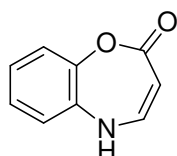
8-Ethylquinolin-4-one **2.65**



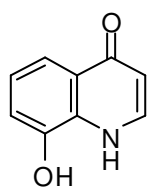
Pyrolysis of 5-[(2-ethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.49** (0.534 g, T_f 600 °C, T_i 140 °C, t 45 min, P 2.7×10^{-2} Torr) gave 8-ethylquinolin-4-one **2.65** as a pale yellow solid (0.320 g, 94%); mp 166 – 168 °C (from ethanol); δ_H (d_6 -DMSO) 11.15 (1H, s, br), 7.99 (1H, d, 3J 7.5), 7.83 (1H, t, 3J 6.8), 7.50 (1H, d, 3J 7.3), 7.25 (1H, t, 3J 7.5), 6.07 (1H, d, 3J 7.5), 2.87 (2H, q, 3J 7.5) and 1.24 (3H, t, 3J 7.5); δ_C (d_6 -DMSO) 177.16 (quat), 139.27, 137.79 (quat), 131.97 (quat), 130.52, 126.00 (quat), 122.84, 122.74, 108.51, 23.09 (CH_2) and 14.10 (CH_3); m/z 173 (M^+ , 100%), 158 (72), 145 (15), 130 (16) and 106 (28).

Pyrolysis of 5-[(2-Hydroxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.54**

Pyrolysis of 5-[(2-hydroxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.54** (w 0.1574 g, T_f 500 °C, T_i 230 °C, P $2.7 - 3.2 \times 10^{-2}$ Torr, t 26 min.) gave two products, a yellow-orange solid and a white solid. Distillation of hot chloroform through the U-tube and concentration of the solution gave 1,5-benzoxazepin-2(3H)-one **2.72** as an orange solid (0.0382 g, 40%). Removal of the white solid from the U-tube gave 8-hydroxyquinolin-4-one **2.71** as an off-white solid (0.0320 g, 33%).

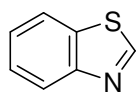


1,5-benzoxazepin-2(3H)-one **2.72**; mp 196 – 198 °C (decomp); (Found M^+ 161.04737, $\text{C}_9\text{H}_7\text{NO}_2$ requires 161.04713); δ_H (360 MHz) 7.19 (1H, br, s), 7.15 – 7.02 (3H, m), 6.83 (1H, dtd, 3J 7.4, 4J 1.2, 5J 0.3), 6.77 (1H, ddd, 3J 9.1, 4J 7.1, 5J 0.5) and 4.98 (1H, ddd, 3J 9.1, 4J 1.5 and 5J 0.5); δ_C (90 MHz) 165.69 (quat), 145.08, 141.58 (quat), 133.36 (quat), 126.34, 125.41, 123.35, 119.70 and 92.62; m/z 161 (M^+ , 100%), 133 (85), 119 (83) and 84 (54).



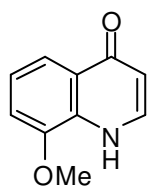
8-Hydroxyquinolinone **2.71**; mp 306 – 308 °C; δ_H (d_6 -DMSO) 7.75 (1H, d, 3J 7.5), 7.50 (1H, dd, 3J 7.3, 4J 1.8), 7.13 – 7.04 (2H, m) and 6.02 (1H, d, 3J 7.3); δ_C (d_6 -DMSO) 176.88 (quat), 147.05 (quat), 138.59, 130.55 (quat), 126.86 (quat), 122.92, 114.32, 114.13 and 108.35.

Pyrolysis of 5-[(2-Mercaptophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.57**



Pyrolysis of 5-[(2-mercaptophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.57** (w 0.3024 g, T_f 600 °C, T_i 200 °C, P 2.9×10^{-2} Torr, t 6 min.) gave a yellow-orange oil, which was absorbed onto silica and purified by column chromatography to give benzothiazole **2.82** as an orange oil (0.0702 g, 48%); bp 66 – 68 °C (2 Torr, lit.⁴⁶ 75 °C, 2 Torr); δ_H (360 MHz) 9.01 (1H, s), 8.16 (1H, d, 3J 8.1), 7.98 (1H, d, 3J 8.1), 7.54 (1H, ddd, 3J 8.4, 4J 7.1, 5J 1.2 and 7.45 (1H, m); δ_C (90 MHz) 153.75, 153.11 (quat), 133.56 (quat), 126.03, 125.41, 123.51 and 121.25; m/z 135 (M^+ , 72%) and 108 (100).

8-Methoxy-1H-quinolin-4-one **2.81**



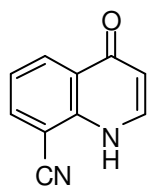
Pyrolysis of 5-[(2-methoxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.55** (w 0.85 g, T_f 500 °C, T_i 160 °C, P $2.6 - 2.8 \times 10^{-2}$ Torr, t 25 min.) gave 8-methoxy-1H-quinolin-4-one **2.81** a pale yellow solid (0.54 g, 99%); mp 210-212 °C (from methanol, lit.³² 219-220 °C); δ_H (360 MHz) 7.82 (1H, d, 3J 7.2), 7.70 (1H, dd, 3J 6.5, 4J 2.9), 7.30 – 7.28 (2H, m), 6.12 (1H, d, 3J 7.6) and 4.30 (3H, s).

Pyrolysis of 5-[(2-Acetoxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.56**

Pyrolysis of 5-[(2-acetoxyphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.56** gave an orange oil, the 1H NMR spectrum of which did not indicate the presence of either the 3 or 8 substituted acetoxyquinolinones and no identifiable

products could be detected.

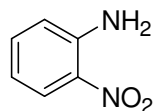
8-Cyano-1*H*-quinolin-4-one **2.86**



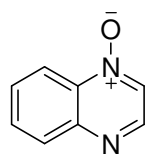
Pyrolysis of 5-[(2-cyanophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.58** (0.604 g, T_f 600 °C, T_i 180 °C, P 2.6 - 3.0 $\times 10^{-2}$ Torr, t 20 min.) gave 8-cyano-1*H*-quinolin-4-one **2.86** as a yellow solid (0.242 g, 64%); mp 234 – 236 °C (decomp, lit.,⁴⁷ 260-262 °C); δ_H 8.43 (1H, dd, 3J 8.0, 4J 1.7), 8.25 (1H, dd, 3J 7.6, 4J 1.7), 8.00 (1H, d, 3J 7.2), 7.51 (1H, t, 3J 7.1) and 6.32 (1H, d, 3J 7.1).

Pyrolysis of 5-[(2-nitrophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.59**

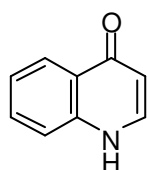
Pyrolysis of 5-[(2-nitrophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.59** (w 0.226 g, T_f 600 °C, T_i 160 °C, P 2.5 – 2.6 $\times 10^{-2}$ Torr, t 55 min.) gave a yellow-brown pyrolysate which was dissolved in acetone and purified by column chromatography to give the following products:



2-Nitroaniline (elution with DCM, 0.004 g, 3%); δ_H 8.12 (1H, dd, 3J 8.6, 4J 1.4); 7.32 (1H, t, 3J 7.3), 6.81 (1H, dd, 3J 8.6, 4J 1.4), 6.71 (1H, t, 3J 7.3) and 6.02 (2H, s, br). NMR spectrum matches previously reported data.⁴⁸

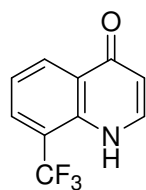


Quinoxaline-*N*-oxide 2.87 (elution with ethyl acetate, 0.012 g, 12%); δ_H 8.63 (1H, d, 3J 3.5), 8.57 (1H, dd, 3J 9.1, 4J 1.6), 8.29 (1H, d, 3J 3.5), 8.07 (1H, dd, 3J 8.6, 4J 1.6) and 7.78 – 7.67 (2H, m). NMR spectrum matches previously reported data.³⁴



Quinolin-4-one 2.90 (elution with methanol, 0.0397 g, 32%); δ_H (d_6 -DMSO) 8.11 (1H, dd, 3J 7.5, 4J 1.4), 7.95 (1H, d, 3J 7.4), 7.57 – 7.52 (2H, m), 7.24 (1H, t, 3J 8.1) and 6.07 (1H, d, 3J 7.4). NMR spectrum matches previously reported data.⁴⁹

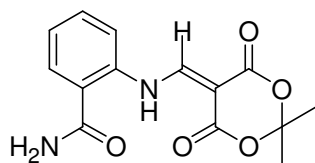
8-Trifluoromethylquinolinone **2.91**



Pyrolysis of 5-[(2-trifluoromethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.60** (w 0.5130 g, T_f 600 °C, T_i 160 °C, P 2.1 – 2.9 10^{-2} Torr, t 35 min) gave 8-trifluoromethylquinolinone **2.91** (0.3706 g, 99%); mp 166 – 168 °C (lit.,³⁵ 174 – 176 °C); δ_H (d_6 -DMSO) 11.38 (1H, s, br), 8.48 (1H, d, 3J 8.1), 8.13 (1H, d, 3J 7.4), 7.96 (1H, br, m), 7.34 (1H, t, 3J 7.4) and 6.19 (1H, br, m).

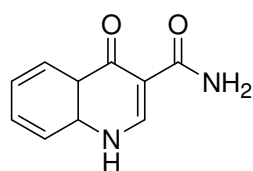
Pyrolysis of 2-Carboxamidoanilinomethylene Meldrum's Acid Derivatives

5-[(2-Carboxamidomethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.61**



Using general method A, 2-aminobenzamide (0.340 g, 2.5 mmol) gave 5-[(2-carboxamidomethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.61** as a yellow solid (0.725 g, 99%); mp 189 – 191 °C; (Found C, 58.20; H, 4.75; N, 10.0. $C_{14}H_{14}N_2O_5$ requires C, 58.0; H, 4.85; N, 9.65 %); δ_H 8.71 (1H, d, 3J 14.6), 8.38 (1H, s, br), 7.89 – 7.86 (2H, m), 7.56 (1H, t, 3J 8.1), 7.42 (1H, t, 3J 7.6) and 1.73 (6H, s); δ_C 169.63, 163.39, 163.33, 152.18, 138.87, 133.11, 129.29, 125.66, 122.72, 117.68, 104.33, 88.21 and 26.90 (2CH₃); m/z 290 (M^+ , 17%), 232 (36), 186 (48), 146 (100) and 119 (29).

3-Carboxamidoquinolin-4-one **2.97**



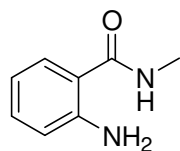
Pyrolysis of 5-[(2-carboxamidomethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.61** (w 0.350 g, T_f 600 °C, T_i 190 °C, P 2.6 – 3.0 $\times 10^{-2}$ Torr, t 30 min) gave 3-carboxamido-1H-quinolin-4-one **2.97** (0.185 g, 81%); mp 193 – 196 °C; δ_H (d_6 -DMSO) 8.18 – 8.14 (2H, m), 7.84 (1H, dd, 3J 6.9, 4J 1.6), 7.70 (1H, d, 3J 7.1) and 7.55 (1H, t, 3J 7.1); δ_C (d_6 -DMSO) 161.23 (quat), 139.23 (quat), 138.06, 132.02, 125.23, 124.78 (quat), 123.96, 118.66 and 114.18 (quat), one quat. missing; m/z 188

(M⁺, 27%), 160 (43), 146 (100), 119 (64) and 92 (22).

Solution Phase Pyrolysis of Compound 2.61

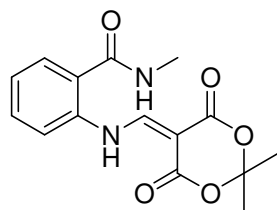
Compound **2.61** (0.1 g) was added to a refluxing solution of Dowtherm A (1 cm³) and maintained at reflux for 20 min. The solution was allowed to cool and the product precipitated using petroleum ether (25 cm³). Collection by filtration gave 3-carboxamidoquinolin-4-one **2.97** as a brown solid; Spectral data as previously reported above.

2-Amino-*N*-methyl-benzamide³⁷ 2.100



Isatoic anhydride (8.10 g, 50 mmol) was added to a solution of methylamine in water (40%, 60 cm³) and the solution was stirred for 20 min. HCl (2M, 20 cm³) was added and the product extracted using ethyl acetate three times. The organics were combined, washed with water (50 cm³), dried over MgSO₄ and the solvent removed to give a white solid (3.01 g, 40%); δ_H 7.29 (1H, dd, ³*J* 7.8, ⁴*J* 1.5), 7.20 (1H, dt, ³*J* 7.2, ⁴*J* 1.5), 6.65 (1H, dt, ³*J* 8.3, ⁴*J* 1.2), 6.61 (1H, dd, ³*J* 6.0, ⁴*J* 1.0), 6.23 (1H, br, s), 5.50 (2H, br, s) and 2.94 (3H, d, ³*J* 4.9).

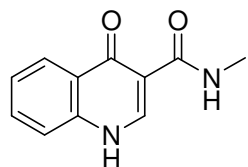
5-[(2-*N*-Methylcarboxamidophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione 2.107



Using general method A, 2-amino-*N*-methyl-benzamide (1.49 g, 10 mmol) gave 5-[(2-*N*-methylcarboxamidophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.107** as a yellow solid (3.03 g, 99%); mp 161 – 163 °C (from ethanol); (Found C, 58.9; H, 5.25; N, 9.25. C₁₅H₁₆NO₅ requires C, 59.2; H, 5.25; N, 9.2) δ_H 13.30 (1H, d, ³*J* 14.6), 8.62 (1H, d, ³*J* 14.6), 7.63 (1H, dd, ³*J* 7.6, ⁴*J* 1.5), 7.52 (1H, td, ³*J* 7.1, ⁴*J* 1.0), 7.40 (1H, t, ³*J* 7.6), 7.23 (1H, t, ³*J* 7.1), 6.72 (1H, br, d, ³*J* 5.3), 3.02 (3H, d, ³*J* 5.3) and 1.72 (6H, s); δ_C 167.46 (quat), 164.17 (quat), 163.62 (quat), 150.88, 138.53 (quat), 132.48, 127.71, 125.39, 122.95 (quat), 116.54, 104.59 (quat), 88.48 (quat), 26.96 (2CH₃) and 26.75 (CH₃); *m/z* 304 (M⁺, 6%), 289 (25), 245 (26), 200 (24),

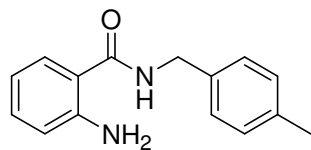
160 (100) and 132 (71)

3- *N*-Methylcarboxamidoquinolin-4-one **2.113**



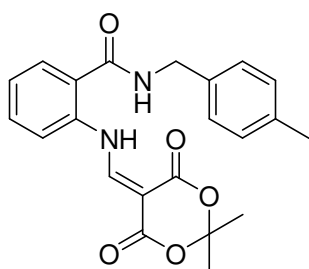
Pyrolysis of 5-[(2-*N*-methylcarboxamidophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxine-4,6-dione **2.107** (w 0.592 g, T_f 600 °C, T_i 190 °C, P $2.6 - 3.6 \times 10^{-2}$ Torr, t 35 min.) gave 3-*N*-methylcarboxamidoquinolin-4-one as a brown solid (0.313 g, 80%); mp 121 – 123 °C (from ethanol); [Found (M-H)⁻ 201.06644, C₁₁H₉N₂O₂ requires 201.06585] δ_H 8.24 (1H, ddd, 3J 8.0, 4J 1.6, 5J 0.7), 8.05 (1H, s), 7.76 – 7.67 (2H, m), 7.50 (1H, ddd, 3J 8.1, 4J 6.5, 5J 1.6) and 3.55 (3H, s); δ_C 161.42 (quat), 148.08 (quat), 146.61, 134.01, 127.28, 127.15, 126.37, 121.80 (quat), 33.89 (CH₃), 2 quat. carbon not apparent; m/z (+ve ESI) 202 (M⁺, 12%).

2-Amino-*N*-(4-methylbenzyl)-benzamide **2.101**



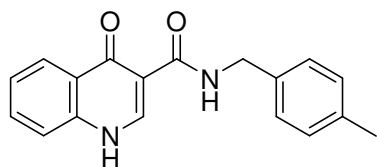
4-Methylbenzylamine (1.23 g, 10.15 mmol) was added to a solution of isatoic anhydride (1.5 g) in DMF (9 cm³). The mixture was stirred overnight at room temperature. The mixture was added to ice-water (150 cm³) and the white precipitate filtered to give 2-amino-*N*-(4-methylbenzyl)-benzamide **2.101** as an off-white solid (1.67 g, 75%); mp 78 – 80 °C; δ_H 7.39 – 7.13 (6H, m), 6.69 (1H, d, 3J 8.3), 6.63 (1H, t, 3J 7.6), 6.31 (1H, br, s), 5.56 (2H, br, s), 4.57 (2H, d, 3J 6.1) and 2.36 (3H, s); δ_C 168.92 (quat), 148.66 (quat), 137.10 (quat), 135.04 (quat), 132.16, 129.27 (2CH), 127.66 (2CH), 126.91, 117.14, 116.38, 115.71 (quat), 43.34 (CH₂) and 20.92 (CH₃); m/z 240 (M⁺, 22%) and 120 (100). Compound was further characterized by its Meldrum's acid derivative **2.108** below.

5-[(2-*N*-(4-Methylbenzyl)carboxamidophenylamino)-methylene]-2,2-dimethyl-[1,3] dioxane-4,6-dione **2.108**



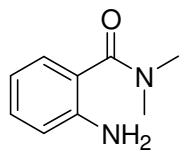
Using general method A, 2-amino-*N*-(4-methylbenzyl)-benzamide (0.480 g, 2 mmol) gave 5-[(2-*N*-(4-methylbenzyl)carboxamidophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.108** as an orange solid (0.785 g, 99%); mp 189 – 191 °C (from ethanol); (Found $M+NH_4^+$ 412.18567; $C_{22}H_{22}N_2O_5 \cdot NH_4$ requires 412.18670); δ_H 13.24 (1H, d, 3J 14.4), 8.55 (1H, d, 3J 14.4), 7.61 (1H, d, 3J 8.7), 7.48 (1H, t, 3J 7.3), 7.38 (1H, d, 3J 8.0), 7.22 – 7.00 (5H, m), 4.56 (2H, d, 3J 5.5), 2.28 (3H, s) and 1.71 (6H, s); δ_C 166.71 (quat), 164.26 (quat), 163.62 (quat), 150.86, 138.68 (quat), 137.28 (quat), 134.57 (quat), 129.29, 127.99, 127.89 (quat), 125.42, 122.89, 116.53, 104.64 (quat), 88.56 (quat), 43.70 (CH₂), 27.04 (2CH₃) and 20.99 (CH₃); m/z (+ve ESI) 412 ($M+NH_4^+$, 15%).

3-*N*-(4-Methylbenzyl)carboxamidoquinolin-4-one **2.114**



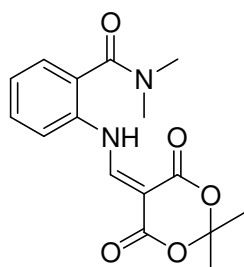
Pyrolysis of 5-[(2-*N*-(4-methylbenzyl)carboxamido phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.108** (w 0.405 g, T_f 600 °C, T_i 200 °C, P 2.3 – 2.8×10^{-2} Torr, t 27 min.) gave 3-*N*-(4-methylbenzyl)carboxamidoquinolin-4-one **2.114** as an orange solid (0.1695 g, 56%); (Found M^+ 292.12065, $C_{18}H_{16}N_2O_2$ requires 292.12063); mp 124 – 126 °C; δ_H (360 MHz) 8.34 (1H, dd, 3J 8.1, 4J 1.3), 8.12 (1H, s), 7.79 – 7.68 (2H, m), 7.51 (1H, ddd, 3J 8.4, 4J 6.9, 5J 1.7), 7.26 (2H, d, 3J 8.3), 7.16 (2H, d, 3J 8.0), 5.16 (2H, s) and 2.33 (3H, s); δ_C (90 MHz) 160.95 (quat), 147.86 (quat), 146.26, 138.06 (quat), 134.15, 132.58 (quat), 129.56 (2CH), 127.93 (2CH), 127.31, 127.22, 126.77, 122.09 (quat), 49.31 (CH₂) and 20.99 (CH₃), two quat. carbon not apparent; m/z 292 (M^+ , 12%), 250 (69), 120 (26) and 105 (100).

2-Amino-*N,N*-dimethylbenzamide⁵⁰ 2.102



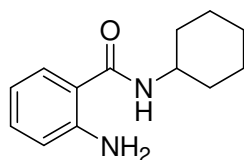
Isatoic anhydride (4.05 g, 50 mmol) was added to a solution of methylamine in water (25%, 48 cm³) and the solution was stirred for 1 h. HCl (2M, 20 cm³) was added and the product was extracted using ethyl acetate (3 × 30 cm³). The organic extracts were combined, washed with water (20 cm³), dried over MgSO₄ and the solvent removed to give an orange oil (2.81 g, 69%); δ_H 7.17 (2H, m), 6.71 – 6.64 (2H, m), 4.49 (2H, s, br) and 3.02 (6H s); m/z 164 (M⁺, 64%), 120 (100) and 92 (39).

5-[(2-*N,N*-Dimethylcarboxamidophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione 2.110



Using general method A, 2-amino-*N,N*-dimethyl-benzamide (0.418 g, 2.5 mmol) gave 5-[(2-*N,N*-dimethylcarboxamido phenylamino)-methylene]-2,2-dimethyl-[1,3]-dioxane-4,6-dione **2.110** as a yellow solid (0.753 g, 95%); mp 130 – 131 °C (from ethanol); (Found M⁺ 318.12004, C₁₆H₁₈N₂O₅ requires 318.12102); δ_H 11.78 (1H, br, d, ³*J* 14.0), 8.64 (1H, d, ³*J* 14.0), 7.53 – 7.25 (4H, m), 3.18 (3H, br, s), 2.99 (3H, br, s) and 1.73 (6H, s); δ_C 167.71 (quat), 164.70 (quat), 163.35 (quat), 151.88, 135.44 (quat), 130.87, 128.47, 126.76 (quat), 125.86, 116.41, 104.90 (quat), 88.14 (quat), 38.78 (CH₃, br), 35.04 (CH₃, br) and 26.89 (2CH₃); m/z 318 (M⁺, 89%), 261 (100), 217 (53), 172 (64), 159 (69) and 116 (44).

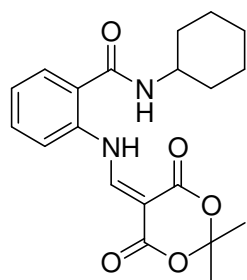
2-Amino-*N*-cyclohexylbenzamide 2.103



Cyclohexylamine (0.545 g) was added to a solution of isatoic anhydride (0.816 g) and DMAP (0.061 g) in DMF (10 cm³). The mixture was stirred overnight, added to ice-water and the white precipitate filtered off. The precipitate was dissolved in ethyl acetate, dried over MgSO₄ and the solvent removed under vacuum to give a white solid (0.782 g, 72%); δ_H 7.28 (1H, dd, ³*J* 7.8, ⁴*J* 1.5), 7.18 (1H, ddd, ³*J* 8.7, ⁴*J* 7.2, ⁵*J* 1.5), 6.68 – 6.60 (2H, m), 5.92 (1H, br, m), 5.46 (2H, br, s), 3.92 (1H, m), 2.03 – 1.97 (2H, m), 1.79 – 1.60

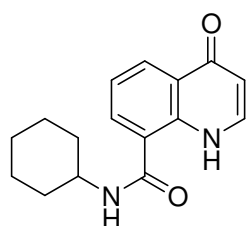
(3H, m), 1.50 – 1.33 (2H, m) and 1.29 – 1.11 (3H, m); δ_C 168.42 (quat), 148.54 (quat), 131.99, 126.96, 117.19, 116.65 (quat), 116.50, 48.25, 33.19 (2CH₂), 22.56 (CH₂) and 24.88 (2CH₂).

5-[(2-*N*-Cyclohexylcarboxamidophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.109**



Using general method A, 2-Amino-*N*-cyclohexylbenzamide (0.436 g, 2 mmol) gave 5-[(2-*N*-cyclohexylcarboxamido phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.109** as a yellow solid (0.746 g, quant.); mp 195 – 197 °C; (Found C; 64.2; H, 6.5; N, 7.65; C₂₀H₂₄N₂O₅ requires C, 64.5; H, 6.45; N, 7.55); δ_H (360 MHz) 13.14 (1H, d, ³*J* 14.4), 8.48 (1H, d, ³*J* 14.4), 7.59 (1H, dd, ³*J* 7.8, ⁴*J* 1.3), 7.45 (1H, t, ³*J* 8.3), 7.35 (1H, d, ³*J* 8.1), 7.15 (1H, t, ³*J* 7.4), 6.69 (1H, d, ³*J* 8.0), 3.97 (1H, m), 1.99 – 1.94 (2H, m), 1.70 – 1.56 (9H, m) and 1.37 – 1.08 (5H, m); δ_C 165.93 (quat), 164.17 (quat), 163.41 (quat), 150.66, 138.33 (quat), 132.25, 127.89, 125.89, 123.48 (quat), 116.27, 104.48 (quat), 88.34 (quat), 48.67, 32.64 (2 CH₂), 26.93 (2 CH₃), 25.25 (CH₂) and 24.73 (2 CH₂); *m/z* 372 (M⁺, 15%), 314 (24), 270 (19), 186 (40), 172 (50) and 147 (100).

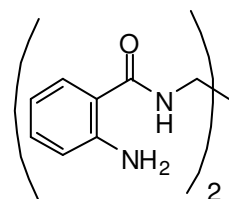
8-*N*-Cyclohexylcarboxamidoquinolin-4-one **2.116**



Pyrolysis of 5-[(2-*N*-cyclohexylcarboxamidophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.109** (w 0.2045 g, *T_f* 600 °C, *T_i* 220 °C, *P* 2.2 – 2.3 × 10⁻² Torr, *t* 27 min.) gave a yellow solid, which was recrystallised from ethyl acetate to give 8-*N*-cyclohexylcarboxamidoquinolin-4-one **2.116** as an off-white solid (0.0088 g, 6%); mp 251 – 254 °C (from ethyl acetate); (Found M⁺ 270.13635, C₁₆H₁₈N₂O₂ requires 270.13628); δ_H (360 MHz) 12.28 (1H, br, s), 8.49 (1H, dd, ³*J* 8.1, ⁴*J* 1.3), 7.84 (1H, dd, ³*J* 7.4, ⁴*J* 1.3), 7.68 (1H, dd, ³*J* 7.4, ⁴*J* 6.4), 7.27 (1H, t, ³*J* 7.9), 6.59 (1H, br, d, ³*J* 6.6), 6.33 (1H, dd, ³*J* 7.4, ⁴*J* 1.0), 4.00 (1H, m), 2.12 – 2.02 (2H, m) and 1.89 – 1.18 (8H, m); δ_C (90 MHz) 178.17 (quat), 167.09 (quat), 139.97 (quat), 138.24, 130.52, 129.67, 127.37 (quat), 121.92, 119.31 (quat) 110.45, 49.04, 32.85 (2CH₂),

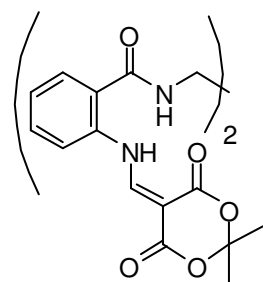
25.34 (CH₂) and 24.80 (2CH₂); *m/z* 270 (M⁺, 100%), 188 (16) and 171 (94).

Bis-*N,N'*-(2-(Aminobenzoyl)-ethylenediamine 2.104



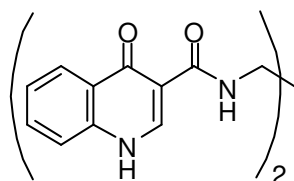
A solution of isatoic anhydride (1.63 g, 10 mmol) and DMAP (0.12 g) in DMF (20 cm³) was cooled to 0 °C and ethylenediamine (0.37 cm³) was added. The mixture was stirred at 0 °C for 2.5 h and room temperature for 2 days. The mixture was poured into ice-water (100 cm³) and the white solid filtered off (0.96 g). Extraction of the aqueous layer with ethyl acetate gave a further portion of product (0.43 g, total 1.33 g, 93%); δ_H (*d*₆-DMSO) 8.07 (2H, s, br), 7.24 (2H, d, ³*J* 8.1), 6.93 (2H, t, ³*J* 7.2), 6.53 (2H, d, ³*J* 8.1), 6.28 (2H, t, ³*J* 7.2) and 3.02 (4H, s).

Bis- *N,N'*-(2-(2,2-dimethyl-4,6-dioxo[1,3]dioxane-methyleneamino)-benzoyl)-ethylenediamine 2.111



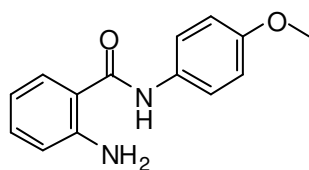
Using general method A, bis- *N,N'*-(2-(aminobenzoyl)-ethylenediamine (0.298 g, 1 mmol) and 2 equivalents of methoxymethylene Meldrum's acid (0.372 g, 2 mmol) gave bis- *N,N'*-(2-(2,2-dimethyl-4,6-dioxo[1,3]dioxane-methyleneamino)-benzoyl)-ethylenediamine **2.111** as an orange solid (0.547 g, 90%); mp 210 – 212 °C (decomp); [Found (M+H⁺) 607.20195, C₃₀H₃₁N₄O₁₀ requires 607.20347]; δ_H (360 MHz, *d*₆-DMSO) 13.00 (2H, br, s), 8.80 – 8.60 (4H, m), 7.91 – 7.75 (4H, m), 7.65 (2H, m), 7.38 (2H, m), 3.60 (4H, s) and 1.74 (12H, s); δ_C (90 MHz, *d*₆-DMSO) 168.74 (2quat), 162.41 (2quat), 151.56 (2CH), 137.93 (2CH), 132.06 (2CH), 130.81 (2CH), 124.96 (2CH), 123.20 (2quat), 117.21 (2quat), 116.98 (2quat), 103.60 (2quat), 87.90 (2quat), 38.79 (2CH₂) and 26.37 (4CH₃); *m/z* (-ve ESI) 605 [M-H, 89%].

***N,N'*-Bis-(4-Oxoquinolin-3-oyl)-ethylenediamine 2.119**



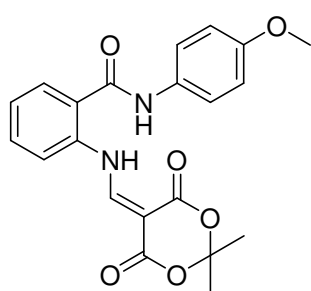
Pyrolysis of bis- *N,N'*-(2-(2,2-dimethyl-4,6-dioxo[1,3]dioxane-methyleneamino)-benzoyl)-ethylenediamine **2.111** (w 0.220 g, T_f 600 °C, T_i 260 °C, P 2.1 – 2.8 $\times 10^{-2}$ Torr, t , 30 min.) gave *N,N'*-bis-(4-oxoquinolin-3-oyl)-ethylenediamine **2.119** as a pale yellow solid (0.102 g, 70%); mp 219 – 220 °C (from ethanol); [Found (M+H)⁺ 403.13806, C₂₂H₁₉N₄O₄ requires 403.14008]; δ_H (360 MHz, d_6 -DMSO) 8.60 (2H, s), 8.06 (2H, dd, 3J 7.5, 4J 1.1), 7.79 (2H, t, 3J 7.1), 7.64 (2H, dd, 3J 8.1, 4J 0.6), 7.52 (2H, t, 3J 7.2) and 4.39 (4H, s); δ_C (90 MHz, d_6 -DMSO) 172.54 (2quat), 160.85 (2quat), 148.22 (2CH), 137.16 (2CH), 127.57 (2CH), 127.45 (2CH), 126.48 (2CH), 121.79 (2quat) and 45.39 (2CH₂), 4 quat. carbon not apparent; m/z (+ve ESI) 403 [(M+H⁺), 28%].

2-Amino-*N*-(4-methoxyphenyl)-benzamide 2.105



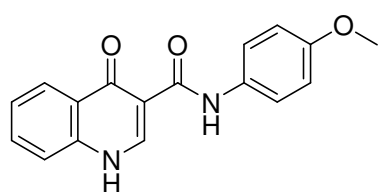
A solution of *p*-anisidine (1.85 g, 15 mmol) and isatoic anhydride (2.41 g, 15 mmol) in DMF (10 cm³) were heated to reflux for 2 h. The solution was allowed to cool, added to water (100 cm³) and extracted three times with ethyl acetate (3 50 cm³). The organics layers were combined, washed with water (2 100 cm³) and brine (100 cm³). The solvent was removed to give 2-amino-*N*-(4-methoxyphenyl)-benzamide **2.105** as a purple solid (3.53 g, 98%); mp 118 – 120 °C (from ethanol, lit. 124 – 126 °C); δ_H 7.38 (2H, d, 3J 9.0), 7.13 (3H, m), 6.81 (2H, d, 3J 9.0), 6.61 (1H, t, 3J 7.4) and 3.73 (3H, s).

5-[(2-*N*-(4-Methoxyphenyl)carboxamidophenylamino)-methylene]-2,2-dimethyl-[1,3] dioxane-4,6-dione **2.112**



Using general method A, 2-amino-*N*-(4-methoxyphenyl)-benzamide (0.484 g, 2 mmol) gave 5-[(2-*N*-(4-methoxyphenyl)carboxamidophenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.112** as an off white solid (0.855 g, quant.); mp; [Found (M+Na)⁺ 419.120078; C₂₁H₂₀NaN₂O₆ requires 419.12136]; δ_H (*d*₆-DMSO) 12.81 (1H, d, ³*J* 14.6) 10.55 (1H, s), 8.72 (1H, d, ³*J* 14.6), 7.94 (1H, dd, ³*J* 7.7, ⁴*J* 1.2), 7.90 (1H, d, ³*J* 8.3), 7.76 – 7.66 (3H, m), 7.47 (1H, t, ³*J* 7.7), 7.01 (2H, d, ³*J* 9.2), 3.81 (3H, s) and 1.72 (6H, s); δ_C (*d*₆-DMSO) 165.46 (quat), 163.42 (quat), 162.87 (quat), 156.05 (quat), 152.52, 138.03 (quat), 132.68, 131.47 (quat), 129.13, 125.50, 124.31 (quat), 122.45 (2CH), 117.99, 113.87 (2CH), 104.16 (quat), 88.02 (quat), 55.26 (CH₃) and 26.59 (2CH₃); *m/z* (+ve ESI) 412 [(M+Na)⁺, 34%].

3-*N*-(4-Methoxyphenyl)carboxamidoquinolin-4-one **2.120**



Pyrolysis of 5-[(2-*N*-(4-methoxyphenyl)carboxamidophenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **2.112** (w 0.5251 g, *T_f* 600 °C, *T_i* 180 °C, *P* 2.7 – 3.6 × 10⁻² Torr, *t* 40 min.) gave a brown solid. Recrystallisation from ethanol gave 3-*N*-(4-methoxyphenyl)carboxamidoquinolin-4-one **2.120** as an off-white solid (0.1665 g, 43%); mp 218 – 221 °C (from ethanol); [Found (M+H)⁺ 295.10846, C₁₇N₁₅N₂O₃ requires 295.10772]; δ_H (360 MHz) 8.38 (1H, d, ³*J* 8.0), 8.12 (1H, s), 7.79 (1H, m), 7.55 (1H, ddd, ³*J* 8.0, ⁴*J* 6.4, ⁵*J* 2.1), 7.34 (2H, d, ³*J* 8.7), 7.22 (1H, m), 7.04 (2H, d, ³*J* 8.9) and 3.87 (3H, s); δ_C (90MHz) 160.97 (quat), 159.82 (quat), 147.81 (quat), 146.32, 134.41, 130.06 (quat), 129.35 (quat), 128.04 (2CH), 127.48, 127.44, 127.06, 123.26 (quat), 122.26 (quat), 114.73 (2CH) and 55.51 (CH₃); *m/z* (+ve ESI) 295 [(M+H)⁺, 32%].

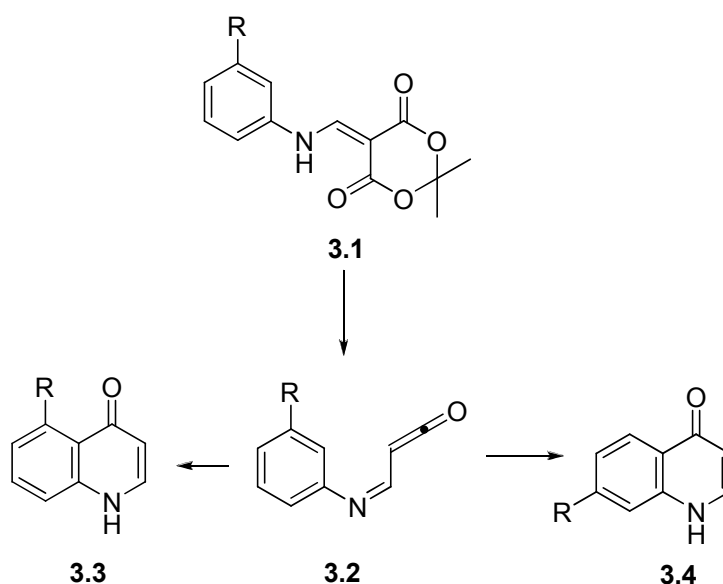
Chapter 3

Pyrolysis of *Meta*-Substituted Anilinomethylene Meldrum's Acid Derivatives

3.1 Discussion

3.1.1 Introduction

As with the *ortho*-substituted analogues, no in-depth study of the effect of substituents on the pyrolysis of *meta*-substituted anilinomethylene Meldrum's acid precursors **3.1** has been carried out. Some FVP experiments have been performed,²⁰ but the yields were very low and almost no regioselectivity was observed. The pyrolysis of **3.1** leads to the formation of the imidoalkyne **3.2**, which can cyclise *ortho* to the substituent to give the 5-substituted product **3.3**, or *para* to give the 7-substituted product **3.4** (Scheme 3.1).



Scheme 3.1 Pyrolysis of compound **3.1**

The ratio of the two regioisomers however could be envisaged to be dependent on the properties of the substituent, such as electronic or steric properties. The steric nature of a group may block the cyclisation *ortho*- to the substituent, forcing the group to cyclise *para*- to it. In comparison, the electronic properties of a group may affect the molecular orbital co-efficients of the aromatic ring, which play a part in the electrocyclisation reaction.

The aim of this chapter was to pyrolyse a range of *meta*-substituted aniline-derived precursors and look for general trends within substituent groups. These substituent

groups can be separated as follows (Table 3.1):

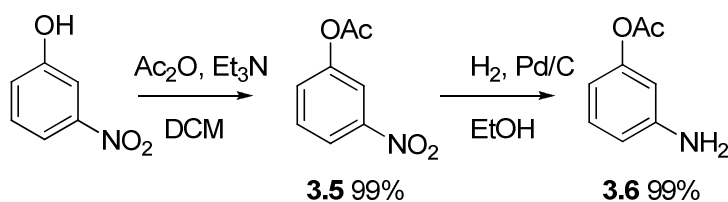
Group	Substituents
Alkyl	Me, Et, ^t Bu
Halogen	F, Cl, Br, I
Electron-Withdrawing (EWG)	CO ₂ Me, CN, NO ₂ , CF ₃ , COMe
Group 6 Substituents	OH, OMe, OAc, SH
Amine	NH ₂ , NHAc, NMe ₂

Table 3.1 List of substituents chosen for the study of the regioselectivity of *meta*-substituted anilinomethylene Meldrum's acid derivatives

Most of the anilines were commercially available, but the few that were not, were synthesised as follows.

3.1.2 Synthesis of Starting Materials

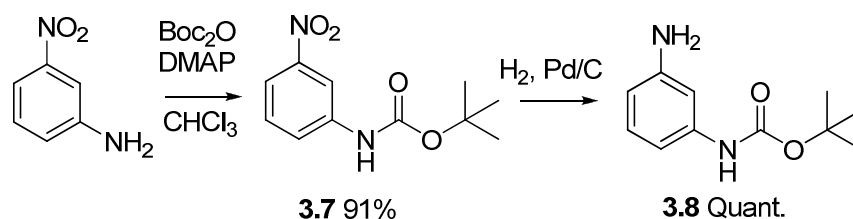
The *O*-acetylated precursor **3.6** was initially synthesised from 3-nitrophenol, which was acetylated using acetic anhydride and triethylamine.⁵¹ Hydrogenation of compound **3.5** using palladium on carbon gave the desired amine in excellent yield (Scheme 3.2)



Scheme 3.2 Synthesis of compound **3.6**

For the NH₂ group, *m*-phenylenediamine could not be used, due to the impossibility of controlling the reaction with methoxymethylene Meldrum's acid to only of the amine groups. Therefore a protecting group that could be easily cleaved would be required for this purpose. It has been previously reported by Storr that *tert*-butoxycarbamates (Boc), under FVP conditions, are deprotected to give the free amine.⁵² The Boc protected *m*-phenylenediamine **3.8** was synthesised as shown in

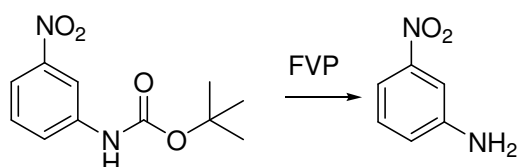
scheme 3.3.



Scheme 3.3 Synthesis of compound **3.8**

Starting with 3-nitroaniline, the protecting group was added using di-*tert*-butyl dicarbonate and dimethylaminopyridine in chloroform to give compound **3.7** in 91% yield. Reduction of the nitro group using palladium on carbon gave the protected *m*-phenylenediamine **3.8** quantitatively.

Storr reported that *N*-Boc groups were deprotected at 600 °C in his apparatus.⁵² To establish the optimum conditions for the Edinburgh set-up, the *N*-Boc protected nitroaniline **3.7** was used a model reaction. The temperature profile is shown below (Figure 3.1)



Scheme 3.4 Deprotection of compound **3.7** under FVP conditions

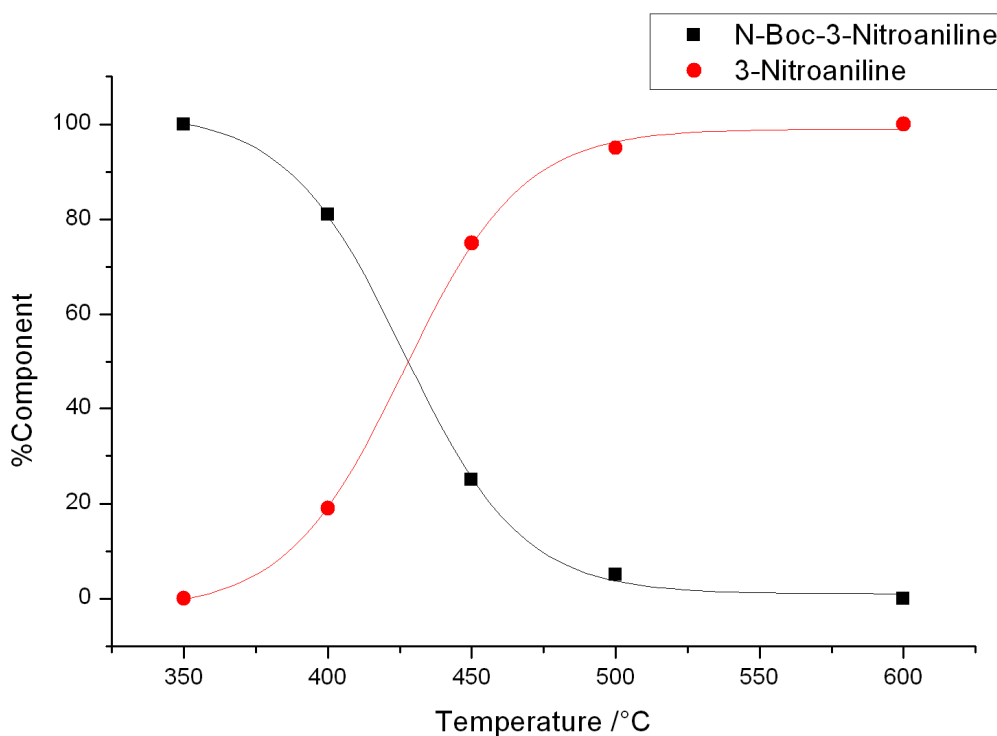
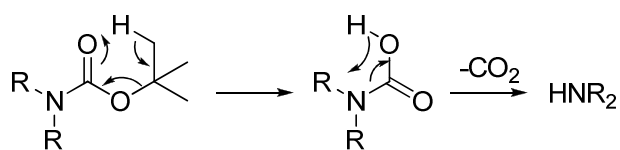


Figure 3.1 Temperature profile for the pyrolysis of compound **3.7**

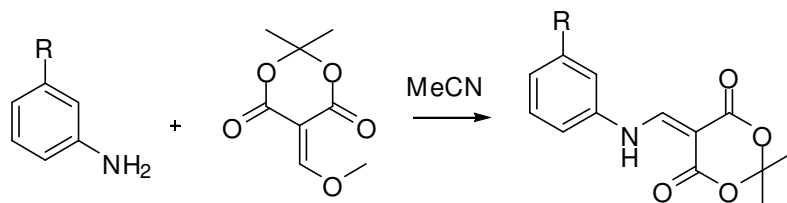
The optimum temperature for the deprotection was found to be 600 °C. The mechanism for the deprotection of Boc groups under FVP conditions is shown in scheme **3.5**.



Scheme 3.5 Mechanism for the loss of *N*-Boc groups under FVP conditions

Hence the Boc deprotection will take place under the same conditions as the pyrolysis of Meldrum's acid derivatives. Upon pyrolysis, the Boc group loses isobutene to generate a carbamic acid. Carbamic acids are known to be unstable and readily decarboxylate to give the free amine and carbon dioxide. This provides an alternative method for deprotecting Boc protected amines without the use of strong acids, such as TFA.

With the required amines at hand, the Meldrum's acid precursors were synthesised, using the procedure described in chapter 2, to give compounds of the basic structure shown in scheme 3.6. The sole exception was the NMe₂ substituted product **3.28**, which was synthesised from its hydrogen chloride salt in good yield (Table 1.2).



Scheme 3.6 General reaction scheme for the synthesis of compounds **3.9 – 3.28**

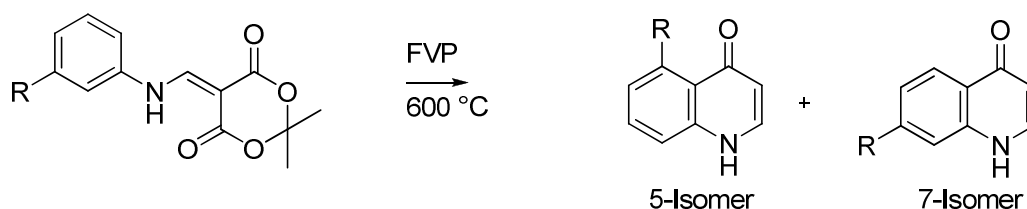
Group	Substituent, X	Compound No.	Yield /%
Alkyl	Me	3.9	98
	Et	3.10	99
	^t Bu	3.11	92
Halogen	F	3.12	66
	Cl	3.13	97
	Br	3.14	80
	I	3.15	95
EWG	CO ₂ Me	3.16	90
	CN	3.17	94
	NO ₂	3.18	98
	CF ₃	3.19	94
	COMe	3.20	87
	Pyridyl (CH = N)	3.21	96
Phenolic	OH	3.22	83
	OMe	3.23	86
	OAc	3.24	75
	SH	3.25	89
Amine	NHBoc	3.26	99
	NHAc	3.27	92
	NMe ₂	3.28	95

Table 3.2 Yields for the synthesis of compounds **3.9 – 3.28**

3.1.3 Pyrolysis of *Meta*-substituted anilinomethylene Meldrum's Acid Derivatives.

Compounds **3.9** – **3.28** were pyrolysed under FVP conditions. As previously stated, the cyclisation of the ketene can occur either *ortho* or *para* to the substituent, giving the 5- or 7- substituted quinolinones respectively. The furnace temperature was set to 650 °C initially.

The ratios of the two isomers were measured from the ^1H NMR spectrum of the crude pyrolysate, by comparison of the integrals of the two compounds. Using multiple integrations on a typical spectrum, the error in measuring the integral was found to be approximately $\pm 5\%$. If these errors are considered, then for the most substituents, the differences between them are sufficiently small that they may be within experimental error. Typically the proton in the 3-position of the quinolinone was used, which shows a resonance at around $\delta_{\text{H}} = 6.5$ ppm of the spectrum. The two compounds could be differentiated by the presence of either a *meta*-coupled singlet (for the 5-isomer) or a triplet (for the 7-isomer) in the ^1H NMR spectrum of the mixture. Table **3.3** gives the isomer ratios for the crude pyrolysates.



Scheme 3.7 Pyrolysis of compounds **3.9** – **3.29**

Group	Substituent, R	Compound Nos.	Yield	7-Isomer /%	5-Isomer /%
Alkyl	Me	3.29, 3.30	89	74 (70*)	26 (30*)
	Et	3.31, 3.32	84	89	11
	tBu	3.33	96	100	0
Halogen	F	3.34, 3.35	85	92	8
	Cl	3.36, 3.37	78	78	22
	Br	3.38, 3.39	48	75	25
	I	3.40, 3.41	77	85	15
EWG	CO ₂ Me	3.42, 3.43	80	82	18
	CN	3.44, 3.45	94	75 (76*)	25 (24*)
	NO ₂	3.46, 3.47	56	83	17
	CF ₃	3.48	99	100	0
	COMe	3.49, 3.50	69	48	52
	Pyridyl (CH = N)	3.51, 3.52	92	87 (80*)	13 (20*)
Phenol	OH*	3.53	55	0	100
	OMe	3.54, 3.55	91	90	10
	OAc**	3.56	99	0	100
	SH	^a	-	-	-
Amine	NHBoc***	3.57	44	0	100
	NHAc**	3.58	44	0	100
	NMe ₂	3.59	54	100	0

Furnace temperatures of * 850 °C, ** 500 °C and *** 600 °C were used

^a ¹H NMR spectrum of the pyrolysate was complex, containing at least 3 significant products

Table 3.3 Yields and isomer ratios for the pyrolysis of *meta*-substituted anilinomethylene Meldrum's acid derivatives **3.9 – 3.28**

From table **3.3**, a range of isomer ratios, from 100% of the 7-isomer to 100% of the 5-isomer was observed. In general however, the ratios are typically around the 4:1 region (*ca.* 80% of the major isomer), with the 7-isomer produced as the major isomer. At higher temperatures (850 °C), the isomer ratios do not deviate significantly from the lower temperature pyrolysis (table **3.3**), showing that temperature does not play a

significant role in determining the isomer ratios and that the reaction mechanism is under thermodynamic, not kinetic, control. The fact that the 7-substituted product is favoured may be due to simple steric effects; the cyclisation *ortho* to the substituent being disfavoured due to steric interactions between the ketene and substituent. As can be seen from table 3.3, both strong electron-withdrawing groups and strong electron-donating groups give similar ratios (MeO, 90% of the 7-isomer vs NO₂, 83% of the 7-isomer).

3.1.4 Discussion of Regioselectivity

In order to attempt to understand the regioselectivity of the reaction, the results were considered as groups of substituents

In the case of the alkyl substituents, a clear pattern is observed. As the steric bulk of the substituent increases, from methyl to *tert*-butyl, the amount of the 5-isomer observed decreases. Pyrolysis of the *tert*-butyl group leads to the formation of the 7-substituted quinolinone exclusively. In the alkyl substituents, the steric properties play a significant role in determining the isomer ratios.

The halogens do not follow a clear pattern, unlike the alkyl substituents. As the size of the halogen increases from F to I, an increase in the amount of the 5-isomer is observed. Then with an iodo substituent, the amount of the 5-isomer decreases. This might be explained by a combination of both steric and other effects. As the halogen is changed from F to I, the amount of the 5-isomer initially increases but with iodo substituents, the steric bulk of the group now becomes more important, forcing the cyclisation towards the *para*-position. In order to investigate the effect of electronic properties of a substituent on a reaction can be shown by a Hammett plot. The Hammett plot for the reaction is shown below (Figure 3.2)

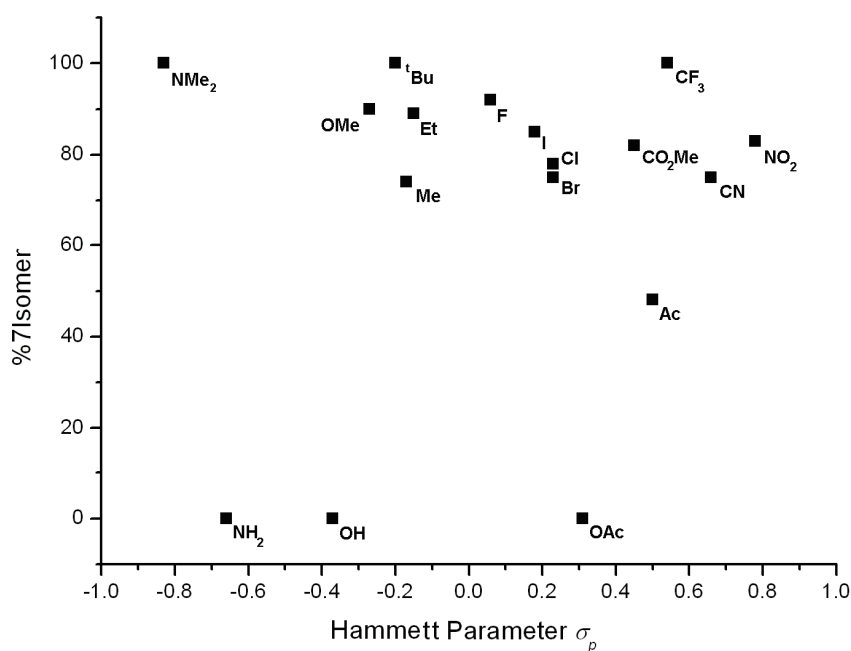


Figure 3.2 Plot of %7-Isomer observed against the Hammett parameter σ_p

The Hammett plot looks like a scatter plot, with no trend between the Hammett parameter and amount of 7-substituted isomer observed. The lack of a trend suggests that electronic effects do not play a substantial role in the regioselectivity of the electrocyclisation reaction.

As previously stated, there are relatively few examples in the literature of the regioselectivity of the pyrolysis of *meta*-substituted anilinomethylene Meldrum's acid derivatives and no general studies, covering a range of substituents, exist. For gas phase pyrolyses, the only real comparative study was reported by Al-Awadi.²⁰ The results reported in this work differ greatly from the work reported by Al-Awadi,²⁰ in both terms of yields and isomer ratios reported. For example, Al-Awadi²⁰ reported that pyrolysis of methoxy- compound **3.23** gave a mixture of 5- and 7-isomers in roughly equal proportions in *ca.* 36% yield, calculated by NMR spectroscopy. In comparison, the crude yield obtained from the pyrolysis of compound **3.23** was 91% (based on pyrolysis of 1.5 g of precursor) and the ¹H NMR spectrum of the material is shown below (figure 3.3).

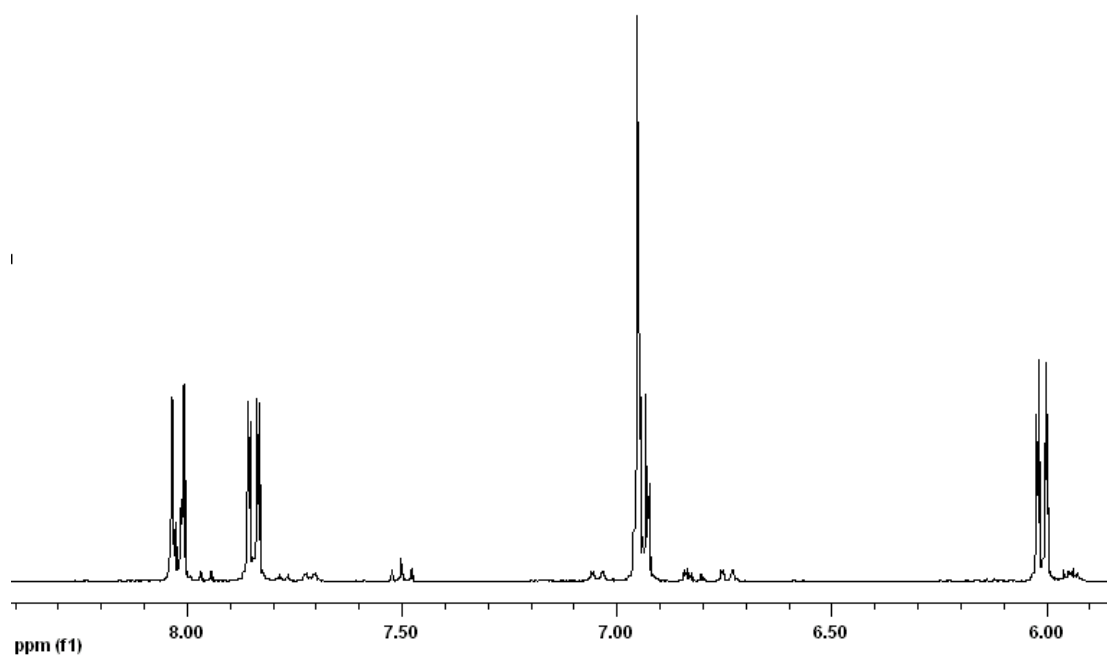


Figure 3.3 ^1H NMR spectrum of the crude pyrolysate, showing the singlet of the major 7-substituted product at $\delta_H = 6.95$ ppm and the triplet of the minor 5-substituted product at $\delta_H = 7.50$ ppm

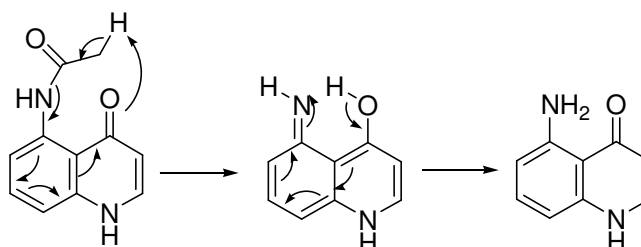
From figure 3.3, one major product can be observed with less than 10% of the minor product. Recrystallisation of this material gave an off-white solid in 62% yield on 0.7 g of precursor and is pure 7-methoxyquinolin-4-one by ^1H NMR spectroscopy. This shows that FVP is a viable route to the 7-substituted quinolinones, with synthetically useful yields on a preparative scale.

The ratios are also different to those reported in the solution phase by Guy.¹⁹ Using microwave heating, the isomer ratios reported were in the range 50:50 (for F) to 85:15 (for PhO) in favour of the 5-substituted quinolin-4-ones. Typically the ratio was around 3:1 in favour of the 5-substituted product.¹⁹ Mixtures were obtained for the trifluoromethyl- substituted compound, whereas under FVP conditions only the 7-substituted product was obtained. The reason for this difference in isomer ratios between solution and gas phase reactions is most likely due to the 1,5 hydrogen shift. In solution phase, the 1,5 shift may occur by an intermolecular process, by-passing the rate-determining step of the reaction. In the gas-phase, the 1,5 shift must occur

and so determines the isomer ratio of the product, as discussed in chapter 2.

3.1.5 Hydrogen bonding examples.

In the previous discussion, a number of substituents showed reversed regioselectivity over the other substituents. These all gave the more sterically crowded 5-substituted quinolinones exclusively. The substituents were NH_2 (derived from the *N*-Boc protected compound), OH, NHAc and OAc. The OH compound required a higher furnace temperature ($850\text{ }^\circ\text{C}$) to form the 5-substituted product and at lower temperatures an alternative isomeric product was formed, which forms the basis of discussion of the next chapter (Compound **4.69**, page 169). The NHAc compound required a lower furnace temperature ($500\text{ }^\circ\text{C}$) to give the 5-substituted quinolinone and at higher furnace temperatures a second product was formed. This was identified as 5-aminoquinolinone **3.57**, formed by deacetylation of the 5-acetamidoquinolinone **3.58**. A possible mechanism for the deacetylation process is shown below (Scheme 3.8).



Scheme 3.8 Mechanism for the loss of acetyl group from 5-acetamidoquinolinone **3.58** to give 5-aminoquinolinone **3.57**

The mechanism proceeds, with loss of the acetyl group as ketene, to give the imine intermediate, which can tautomerise to the amine product. The temperature profile for this reaction is shown below (Figure 3.4).

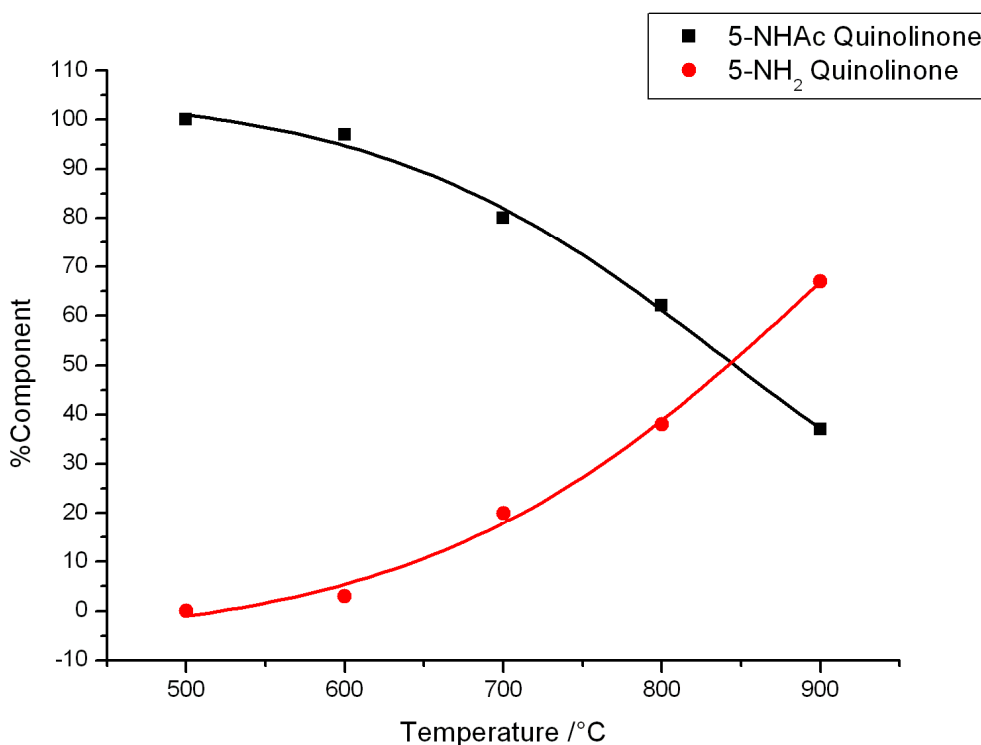
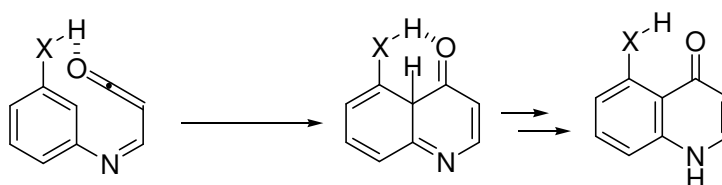


Figure 3.4 Temperature profile for the pyrolysis of compound **3.27**

Due to the observed deacetylation in this pyrolysis, the same furnace temperature (500 °C) was employed for the pyrolysis of the *O*-acetylated precursor **3.24**.

With the exception of the OAc, all these substituents have a hydrogen atom bonded to an electronegative substituent, which in principle may hydrogen bond to the initial ketene, directing it to the 5-position (Scheme **3.9**)



Scheme 3.9 Potential hydrogen bonding interaction of X-H groups

In order to quantify the effect of the amino- and hydroxy- groups on the regioselectivity, DFT calculations were employed at B3LYP/6-31G** level. The energy surfaces for both are shown below (Figures **3.5** and **3.6**, respectively)

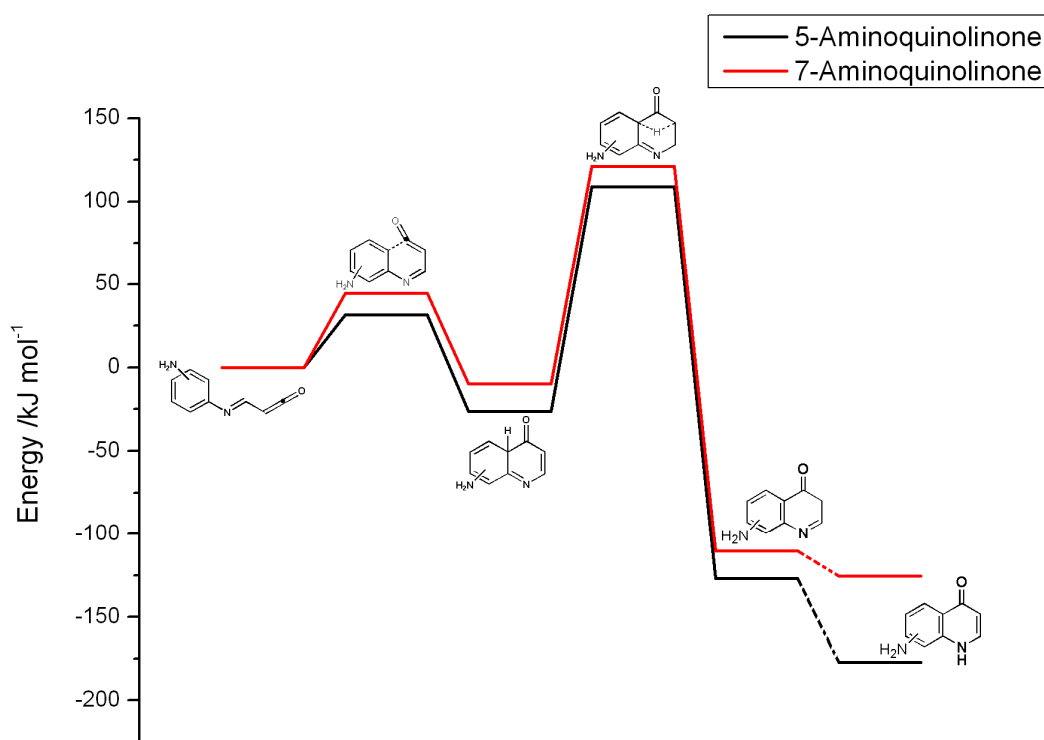


Figure 3.5 Energy surface for the formation of 5- and 7- aminoquinolinones

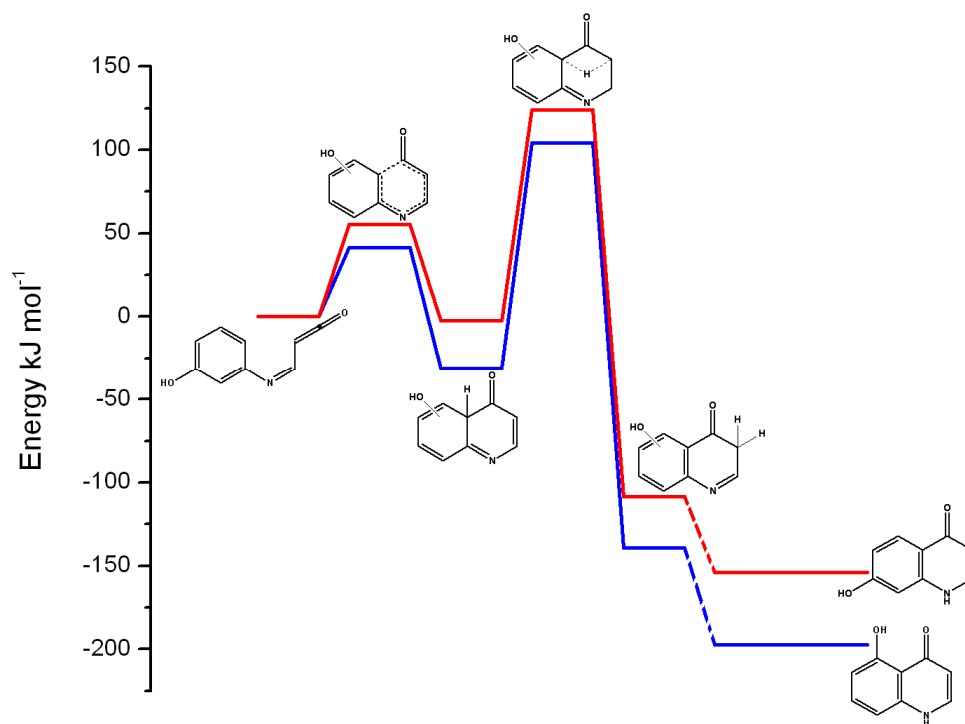
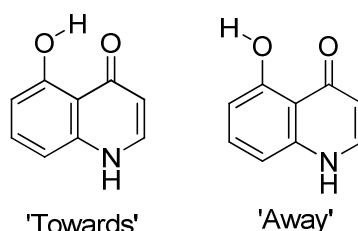


Figure 3.6 Energy surface for the formation of 5- and 7- hydroxyquinolinones

In both examples, the 5-substituted product was shown to be lower in energy across the energy surface. In comparison the 7-substituted products are typically lower in energy for the other substituents that display 'typical' regioselectivity. To demonstrate the effect of the hydrogen bonding, the energy surface for the 5-hydroxy substituted quinolinone was calculated with the hydrogen atom pointing away from the carbonyl group and the energies are shown below in table 3.6

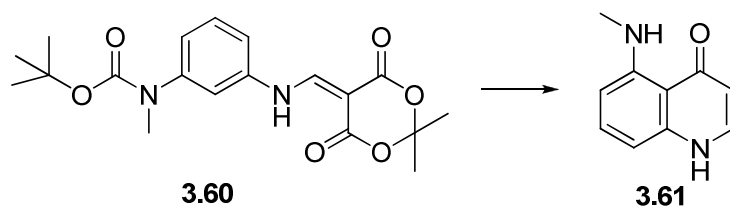


Structure	5-Isomer/Towards	7-Isomer	5-Isomer/Away
Ketene	0	0	0
1 st Transition State	0	15.7	13.9
1 st Intermediate	0	30.4	52.6
2 nd Transition State	0	21.7	38.9
2 nd Intermediate	0	32.5	57.0
Product	0	45.5	70.1

Table 3.5 Calculated energies for the mechanism of the formation of hydroxyquinolinones (Energies are relative to the 5-hydroxyquinolinone, with the hydrogen positioned towards the carbonyl, in kJ mol⁻¹)

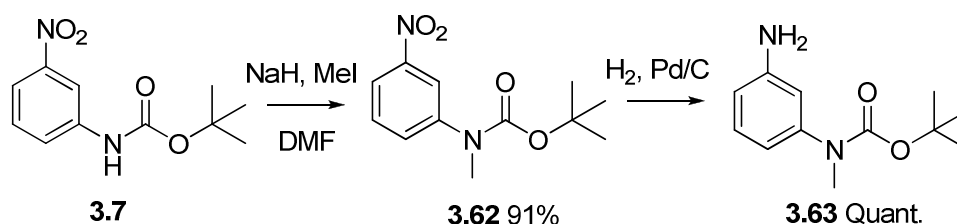
From table 3.5, the effect of the hydrogen bonding is shown. The energies for the 5-substituted quinolinone with the hydrogen atom set to pointing away from the carbonyl group were significantly higher than the other possibility (with the hydrogen atom pointing towards the carbonyl group) or the 7-substituted product. This clearly demonstrates how important this interaction is and why only the 5-substituted product is formed.

As a further example of the effect of hydrogen bonding, pyrolysis of *N*-methyl-*N*-Boc compound 3.60 was studied and should give 5-methylaminoquinolinone 3.61, if hydrogen bonding is important (Scheme 3.10).



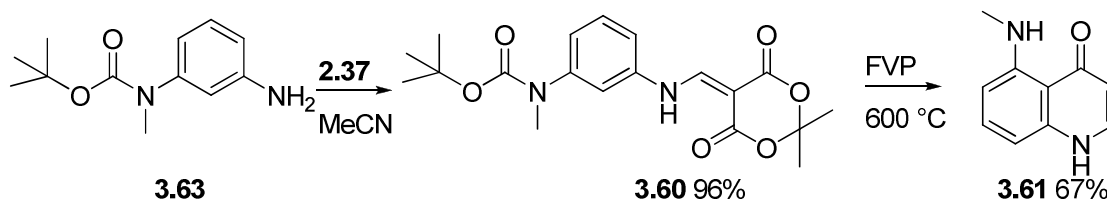
Scheme 3.10 Pyrolysis of compound **3.60**

N-Methylation of *tert*-butyl-(3-nitrophenyl)carbamate **3.7** was performed using sodium hydride and iodomethane in DMF⁵⁶ to give the *tert*-butyl-*N*-methyl-(3-nitrophenyl)carbamate **3.62** in 91% yield without further purification. Hydrogenation using palladium on carbon gave *tert*-butyl-*N*-methyl-(3-aminophenyl)carbamate **3.63** quantitatively (Scheme **3.11**).



Scheme 3.11 Synthesis of compound **3.63**

Using the standard conditions, compound **3.63** was reacted with methoxymethylene Meldrum's acid **2.37** to give compound **3.60** in 96% yield. Pyrolysis of compound **3.60** gave a brown solid at 600 °C, which was identified as 5-methylaminoquinolinone **3.61**, in 67% yield (Scheme **3.12**)

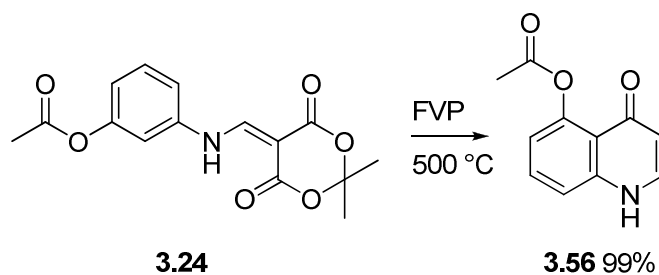


Scheme 3.12 Synthesis and pyrolysis of compound **3.60**

The implication of this result is that the carbamate is deprotected first, then the regioselective cyclisation occurs to give the 5-substituted product exclusively.

3.1.6 Pyrolyses of *N*- or *O*- Acetylated Anilinomethylene Meldrum's Acid Derivatives

As previously stated pyrolysis of the *O*-acetylated compound **3.24** gave the 5-substituted product **3.56** in excellent yield (Scheme 3.13)



Scheme 3.13 Pyrolysis of compound **3.24**

However, unlike the hydroxy- example, there is no immediately obvious explanation for this regioselectivity. In order to study if an *X*-acetyl group had a general effect on the regioselectivity, the *N*-methyl-*N*-acetyl compound **3.64** was chosen as a model system (Figure 3.7).

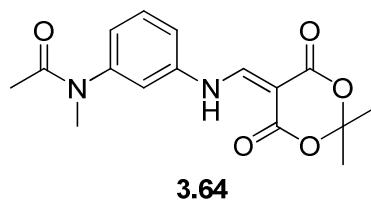
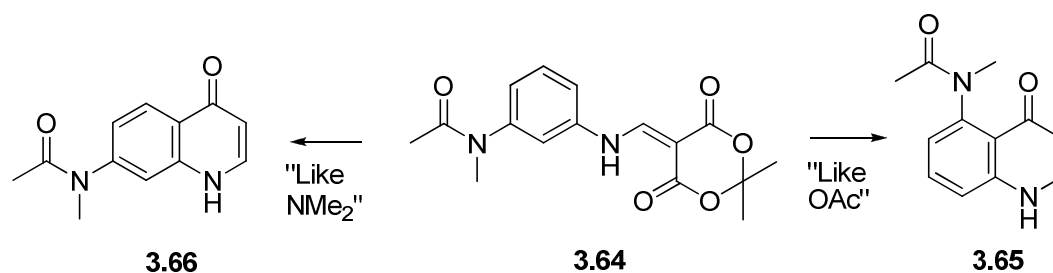


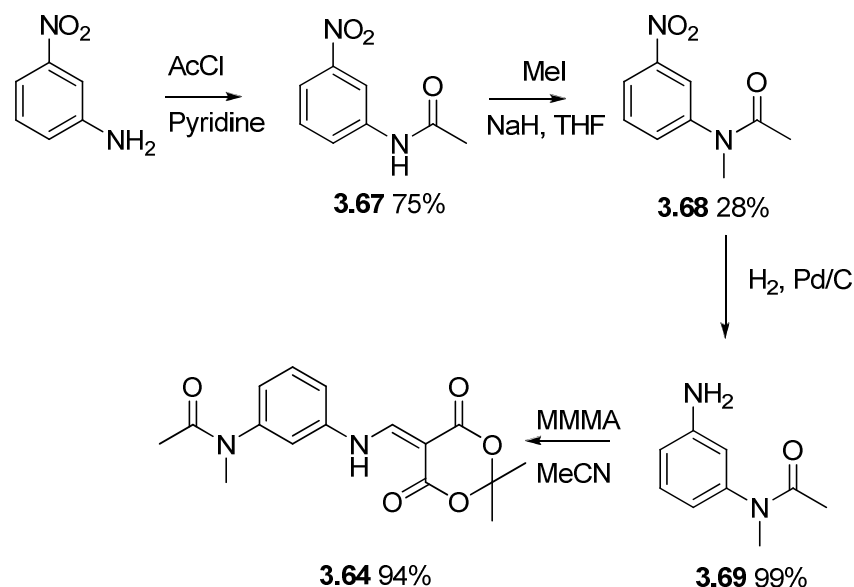
Figure 3.7 Structure of compound **3.64**

Using the analogy of the previous results, the pyrolysis of this compound has a number of possibilities. Unlike the *NHAc* substituted compound, there is no possibility of hydrogen bonding and the *NMe*₂ substituted compound gave only the 7-substituted quinolinone. Compound **3.64** could be imagined to have similar steric properties and may react similarly to give compound **3.66**. On the other hand, if the acetyl group plays a major role in the regioselectivity then the pyrolysis of compound **3.64** should give the 5-substituted quinolinone **3.65** exclusively (Scheme 3.14)



Scheme 3.14 Potential products from the pyrolysis of compound **3.64**

The precursor **3.64** was synthesised as follows: Starting from 3-nitroaniline, acetylation using acetyl chloride in pyridine gave the *N*-acetylated compound **3.67** which was methylated using sodium hydride in THF to give the *N*-methylacetanilide **3.68** in 28% yield. Hydrogenation using palladium on charcoal gave the aminoacetanilide **3.69**, which was reacted with methoxymethylene Meldrum's acid to give compound **3.64** in 94% yield (Scheme 3.15).



Scheme 3.15 Synthesis of compound **3.64**

Pyrolysis of compound **3.64** gave an orange solid, which was isolated in 66% yield. The ^1H NMR spectrum of the entire pyrolysate is shown below (Figure 3.8).

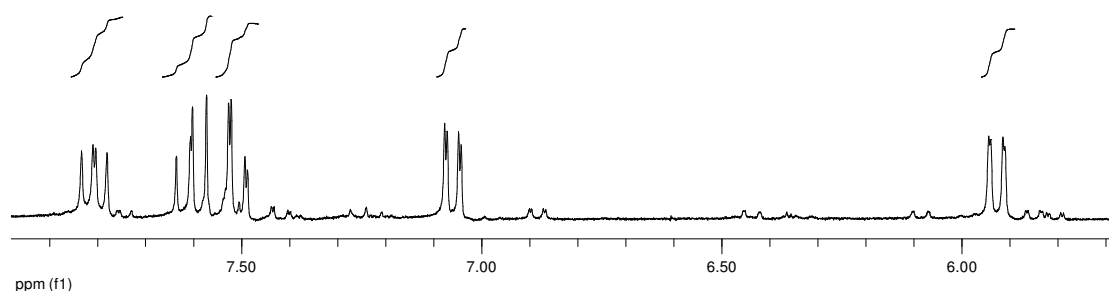


Figure 3.8 ^1H NMR spectrum of the product from the pyrolysis of compound **3.64**

From figure **3.8**, the presence of a triplet at $\delta_H = 7.63$ ppm and the absence of a (*meta*-coupled) singlet indicates that the product formed is the 5-substituted isomer. This shows that the cyclisation is controlled by the acetyl substituent rather than the steric bulk (*cf.* NMe_2 substituent.)

In both examples (OAc and NMeAc), there may be an interaction between the ketene and the carbonyl of the acetyl group (Figure **3.9**)

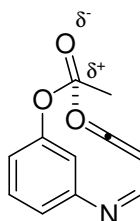


Figure 3.9 Potential interaction between the acetyl and the imidoylketene

In an attempt to rationalise this result, DFT calculations were used at B3LYP/6-31G** level to model the energy surface of the reaction. The energy surface is shown below (Figure **3.10**)

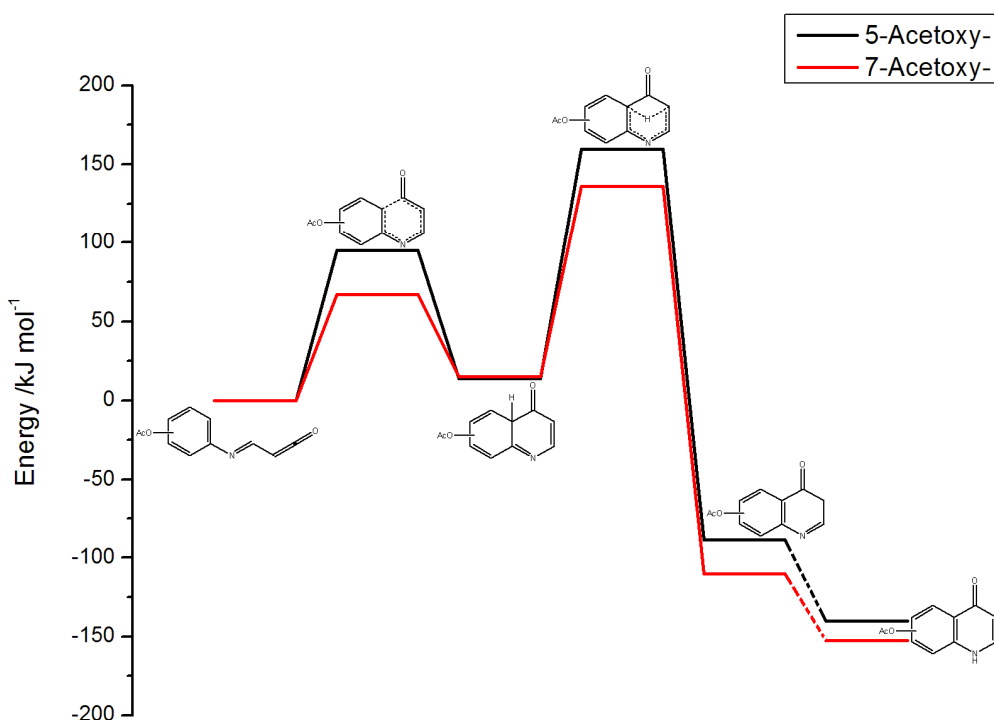


Figure 3.10 Energy surface for the formation of 5- and 7-acetoxyquinolinones

From figure 3.10, it can be seen that the observed 5-substituted product is almost always higher in energy than the unobserved 7-substituted product. The interaction between the carbonyl of the acetyl group and the ketene oxygen was also not observed. In this case, the calculations do not support the results of the experiment and the origins of the regioselectivity of this example remain unknown.

3.1.7 DFT Rationale for the Regioselectivity of the Cyclisation Reaction

In order to rationalise the results for the substituents used in the regioselectivity study, DFT calculations at B3LYP/6-31G** level were employed. In chapter 2, the 1,5 hydrogen shift was shown to be the rate determining step of the mechanism. Therefore it might be envisaged that the difference between the activation energies of the 1,5 hydrogen shift for the two isomers might be an important factor.

However the initial cyclisation is the obvious step which affects the regioselectivity may play an important role in determining the regioselectivity. Therefore a plot of the

difference in the activation energy of the cyclisation against the amount of the 7-substituted product is shown in figure 3.11.

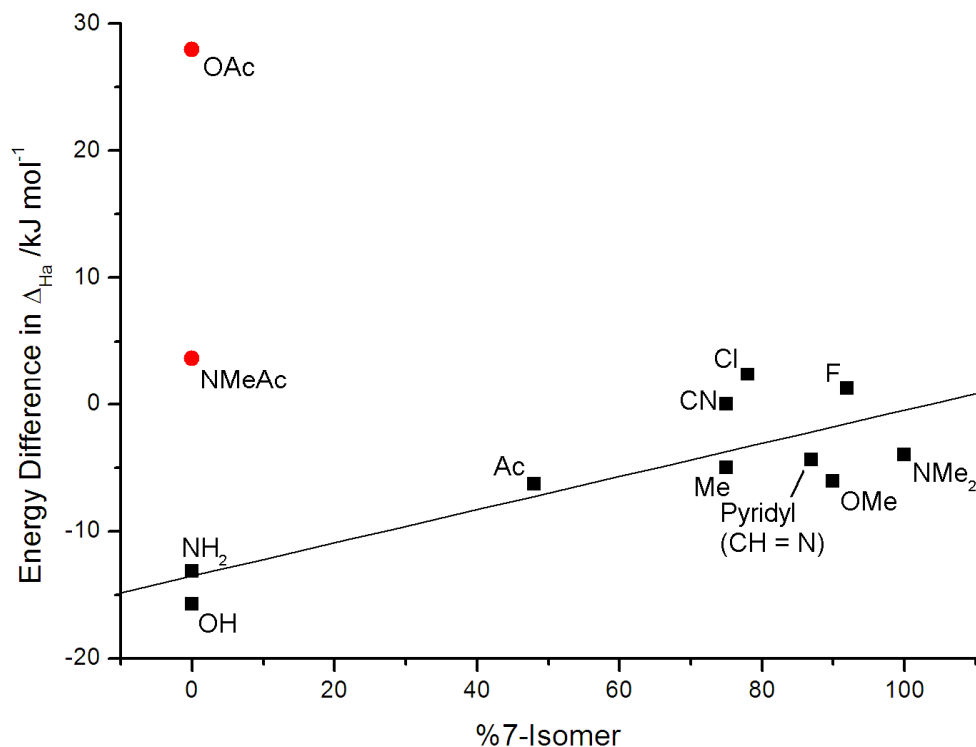


Figure 3.11 Plot of the calculated energy difference in the first transition state (the initial cyclisation) against the observed %7-Isomer

With the exception of the two acetyl (OAc and NMeAc) substituents, there appears to be a trend between the activation energy and the regioselectivity, with a straight line fit of an R value of 0.82. This occurs over a range of approximately 15 kJ mol⁻¹.

In previous energy surfaces, the 1,5 hydrogen shift has been shown to possess a larger energy barrier than the initial cyclisation, indicating that it is the rate-determining process in the reaction mechanism. In order to test whether the 1,5 hydrogen shift plays a more important role, a plot of the difference in activation energies for the 1,5 hydrogen shift against the percentage of the observed 7-substituted product is shown below (Figure 3.12).

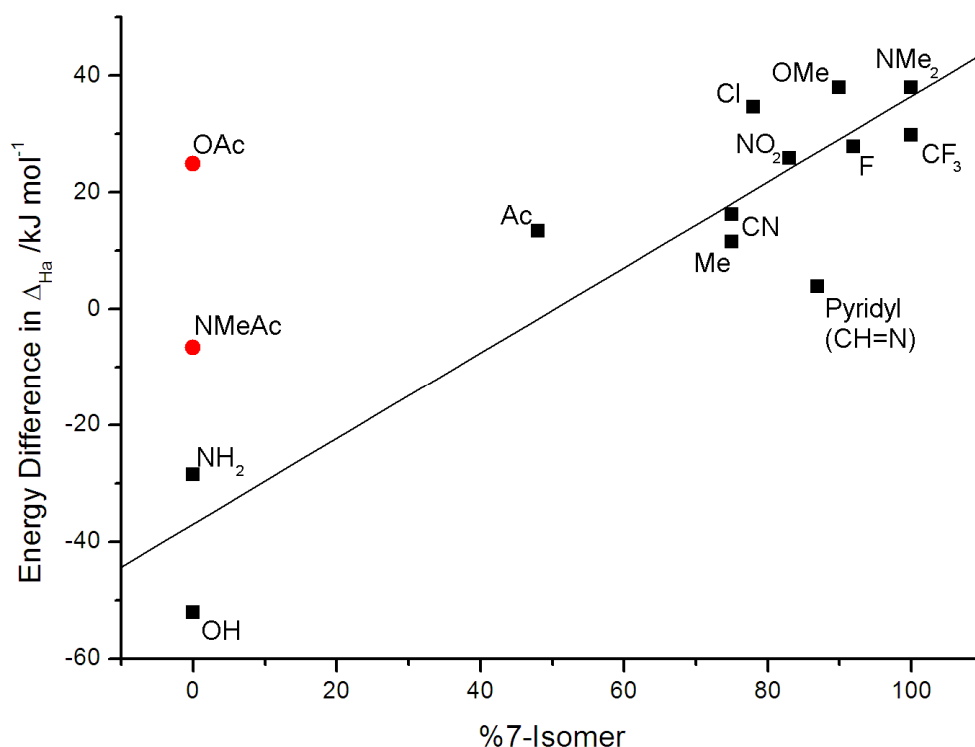


Figure 3.12 Plot of the calculated energy difference in the second transition state (1,5 hydrogen shift) against the observed %7-Isomer

From figure 3.12, we again can see that as the percentage of the 7-substituted product increases, the difference between the activation energies increases, as might be expected. As before, the two acetyl (OAc and NMeAc) substituents are anomalous. The R factor of the straight line fit is 0.91. However the energy range here is approximately 100 kJ mol⁻¹, compared to around 15 kJ mol⁻¹ for the cyclisation reaction. From this result, it can be said that the 1,5 hydrogen shift plays a greater role, under gas phase conditions, in affecting the regioselectivity of the reaction.

The advantage of the use of the calculations in explaining the regioselectivity of a substituent, is that they account for factors which are not explained by steric or electronic factors alone. This helps rationalise why substituents, such as trifluoromethyl- or dimethylamino-, give the observed isomer ratios.

3.2 Conclusion

The regioselectivity of pyrolysis of *meta*-substituted anilinomethylene Meldrum's acid precursors has been studied. For most substituents, the 7-substituted product is formed as the major product, with ratios ranging from 3:1 to 9:1 dependent on substituent. In general, the major isomer can be obtained by recrystallisation of the crude pyrolysate in good yields, providing a good synthetic route into these compounds; this conclusion differs from some reports in the literature.¹⁹

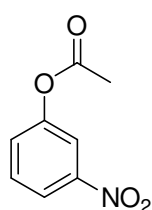
With some substituents, hydrogen bonding interactions between the substituent and the imidoylketene oxygen atom were shown to be an important factor and 'override' the normal regioselectivity, giving the 5-substituted products exclusively. DFT calculations were employed to demonstrate that this was the case. This provides an excellent synthetic route in the 5-substituted quinolinones, which might be difficult to isolate from the crude mixture of 5- and 7-substituted quinolinones usually obtained. It does not provide a route to the 7-substituted analogues, though this may be easily made by other routes, for example the 7-aminoquinolinone might be made by reduction of 7-nitroquinolinone.

While no obvious trend is observed, based on simple steric or electronic properties of the substituent, DFT calculations have shown that the energy barriers of the 1,5 hydrogen shift play an important role in affecting the ratio of the two regioisomers.

3.3 Experimental

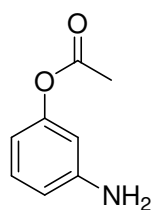
Synthesis of Substituted Anilines

3-Acetoxybenzene⁵¹ 3.5



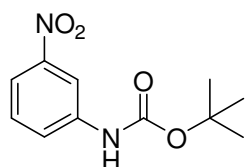
Acetic anhydride (3.8 cm³) and acetic acid (10 drops) were added to an ice cold solution of 3-nitrophenol (3.892 g, 28 mmol) and triethylamine (6.1 cm³) in dichloromethane (20 cm³) and heated at reflux for 0.5 h. The mixture was added to water and the pH adjusted with HCl (1 M) to 5. The organic layer was separated off and the aqueous layer washed with dichloromethane (2 × 30 cm³). The combined organic layers were washed with sodium bicarbonate and water, dried over MgSO₄ and the solvent removed to give the product as a off white solid (5.027 g, 99%); mp 56-57 °C (from light petroleum) (lit.,⁵³ 54 °C) δ_H 8.04 (1H, ddd, ³*J* 8.1, ⁴*J* 2.2, ⁵*J* 1.0), 7.92 (1H, dt, ⁴*J* 2.2, ⁵*J* 0.3), 7.49 (1H, dt, ³*J* 8.1, ⁴*J* 0.3), 7.38 (1H, ddd, ³*J* 8.1, ⁴*J* 2.2, ⁵*J* 1.0) and 2.28 (3H, s); δ_C 169.11 (quat), 151.29 (quat) 149.13 (quat), 130.41, 128.46, 121.13, 117.74 and 22.52 (CH₃).

3-Acetoxyaniline 3.6



A solution of 3-acetoxybenzene (0.453 g, 2.5 mmol) in ethanol (20 cm³) was hydrogenated at 5 bar using Pd/C (49 mg) for 1 h. The solution was filtered through celite and the solvent removed to give the product as an orange oil (0.419 g, quant.); δ_H 7.09 (1H, t, ³*J* 8.1), 6.48 (1H, ddd, ³*J* 8.1, ⁴*J* 2.2, ⁵*J* 0.9), 6.42 (1H, ddd, ³*J* 8.1, ⁴*J* 2.2, ⁵*J* 0.9), 6.36 (1H, t, ⁴*J* 2.2) and 2.23 (3H, s) δ_C 169.92 (quat), 152.05 (quat), 148.08 (quat), 130.37, 113.01, 111.69, 108.63 and 21.53 (CH₃).

tert-Butyl (3-nitrophenyl)-carbamate⁵⁴ 3.7



A solution of di-*tert*-butyl dicarbonate (7.00 g, 32 mmol) in chloroform (24 cm³) was added to a solution of 3-nitroaniline (4.00 g, 29 mmol), triethylamine (4 cm³) and 4-

dimethylaminopyridine (1.78 g, 14.6 mmol) in chloroform (76 cm³). The mixture was then heated at reflux for 5 h. Evaporation of the solvent and purification by dry flash chromatography (Basic alumina, 3:1 Cyclohexane: ethyl acetate eluent) to give *tert*-butyl (3-nitrophenyl)-carbamate (6.11 g, 91%); mp 97-98 °C (from toluene, lit.,⁴⁰ 96-97 °C); δ_H 8.32 (1H, t, 3J 2.2), 7.85 (1H, ddd, 3J 8.2, 4J 2.2, 5J 1.0), 7.68 (1H, dd, 3J 8.2, 4J 1.2), 7.42 (1H, t, 3J 8.2), 6.92 (1H, s) and 1.52 (9H, s); δ_C 152.75 (quat), 149.06 (quat), 140.07 (quat), 130.06, 124.37, 117.94, 113.52, 81.98 (quat) and 28.60 (3CH₃).

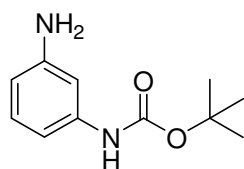
Temperature Profile for the Pyrolysis of *tert*-butyl(3-nitrophenyl)-carbamate

The inlet temperature for these reactions was set at 130 °C. Results are shown in table 3.5 below

T_f /°C	wt /mg	P / $\times 10^{-2}$ Torr	t /min	Carbamate /%	Amine /%
350	50.5	2.6 – 2.9	6	100	0
400	50.2	2.5 – 3.0	8	81	19
450	51.1	2.6 – 3.0	6	25	75
500	49.9	2.6 – 3.0	7	5	95
600	50.0	2.6	7	0	100

Table 3.6 Conditions and results for FVP of compound 3.7

tert-Butyl (3-aminophenyl)-carbamate⁵⁴ 3.8



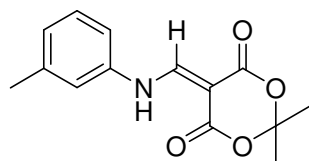
A solution of *tert*-butyl (3-nitrophenyl)-carbamate (0.70 g, 2.5 mmol) in ethyl acetate (25 cm³) was hydrogenated at 5 bar for 4 h using Pd/C (50 mg). The solution was filtered through celite and the solvent was removed to give *tert*-butyl (3-Aminophenyl)-carbamate as an off-white solid (0.70 g, 100%); δ_H 7.02 (1H, t, 3J 8.1), 6.95 (1H, s), 6.57 – 6.52 (2H, m), 6.34 (1H, dd, 3J 8.0, 4J 2.2), 3.64 (2H, s, br) and 1.50 (9H, s); δ_C 153.10 (quat), 147.64 (quat), 139.76 (quat), 130.04, 110.21, 108.96, 105.48, 80.70 (quat) and 28.71 (3CH₃).

Synthesis of Meldrum's acid Precursors

General Procedure

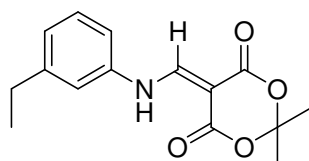
To a solution of the amine (1 equivalent) dissolved in the minimal amount of acetonitrile, was added methoxymethylene Meldrum's acid (1 equivalent). The mixture was allowed to stand for 15 min. and the solvent removed to give the product.

5-[(3-Methylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.9**



Using the general procedure, *m*-toluidine (0.535 g, 5 mmol) gave 5-[(3-methylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.9** (1.279 g, 98%); mp 114- 116 °C (from ethanol); (Found C, 64.25; H, 5.8; N, 5.25. C₁₄H₁₅NO₄ requires C, 64.4; H, 5.7; N 5.4%); δ_H 11.41 (1H, d, 3J 14.4), 8.83 (1H, d, 3J 14.4), 7.49 (1H, t, 3J 7.9), 7.28-7.21 (3H, m), 2.52 (3H, s) and 1.94 (6H, s); δ_C 165.91 (quat), 164.04 (quat), 152.95 (quat), 140.75 (quat), 138.07 (quat), 130.26, 128.06, 118.95, 115.53, 105.53 (quat), 87.39, 27.40 (2CH₃) and 21.76 (CH₃); m/z 261 (M⁺, 60%), 203 (100) 158 (61), 144 (84), 131 (77) and 87 (81).

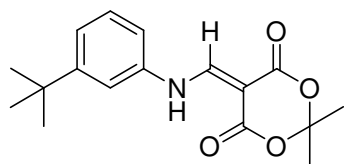
5-[(3-Ethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.10**



Using the general procedure, 3-ethylaniline (1.210 g, 10 mmol) gave 5-[(3-ethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.10** (2.96 g, 99%); mp 78 - 79 °C (from ethanol). (Found C, 65.5; H, 6.25; N, 5.1. C₁₅H₁₇NO₄ requires C, 65.45; H, 6.25; N, 4.75.); δ_H 11.26 (1H, d, 3J 14.4), 8.69 (1H, d, 3J 14.4), 7.37 (1H, t, 3J 7.8), 7.16-7.08 (3H, m), 2.75-2.69 (2H, q, 3J 7.6), 1.79 (6H, s) and 1.30 (3H, t, 3J 7.6). δ_C 166.01 (quat), 164.09 (quat), 153.00, 147.19 (quat), 138.19 (quat), 130.43, 126.99, 117.88, 115.78, 105.59 (quat), 87.43 (quat), 30.12 (CH₂), 27.46 (2CH₃) and 15.79 (CH₃); m/z 275 (M⁺, 19%), 217 (45), 173 (11), 172 (35), 144 (100) and 105 (8).

5-[(3-*tert*-Butylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione

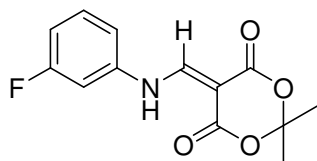
3.11



Using the general procedure, 3-*tert*-butylaniline (1.490 g, 10 mmol) gave 5-[(3-*tert*-butylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.11**

(2.799 g, 92%); mp 136-137 °C (from ethanol). (Found C, 66.7; H, 6.9; N, 4.6. $C_{17}H_{21}NO_4 \cdot 0.2H_2O$ requires C, 66.55; H, 6.85; N, 4.55 %); δ_H 11.94 (1H, d, 3J 13.5), 8.59 (1H, d, 3J 13.5), 7.33-7.14 (3H, m), 7.02 (1H, dt, 3J 7.3), 1.63 (6H, s) and 1.29 (9H, s); δ_C 163.73 (quat), 161.81 (quat), 151.93 (quat), 150.80, 135.67 (quat), 127.89, 122.22, 113.69, 113.04, 103.25 (quat), 85.03 (quat), 33.07 (quat), 29.30 (3CH₃) and 25.12 (2CH₃); m/z 303 (M^+ , 30%), 245 (44), 200 (19), 175 (12), 144 (100).

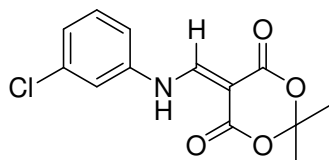
5-[(3-Fluorophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **3.12**



Using the general procedure, 3-fluoroaniline (1.11 g, 10 mmol) gave 5-[(3-fluorophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **3.12** (1.76 g, 66%); mp

152-153 °C (from ethanol); (Found C., 59.1; H., 4.6; N., 5.25. $C_{13}H_{12}FNO_4$ requires C., 58.9; H., 4.55; N., 5.30 %); δ_H 11.21 (1H, d, 3J 14.2), 8.59 (1H, d, 3J 14.2), 7.39 (1H, m), 7.05-6.93 (3H, m) and 1.74 (6H, s); δ_C 165.35 (quat), 163.17 (quat), 161.42 (quat), 152.32, 139.30 (quat), 139.14 (quat), 131.55, 113.73, 105.63, 105.28, 87.86 (quat) and 26.97 (2CH₃); m/z 265 (M^+ , 19%), 207 (57), 163 (39), 162 (100), 135 (98) and 95 (60).

5-[(3-Chlorophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **3.13**

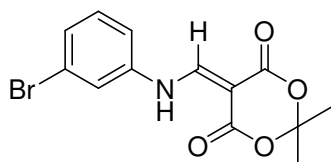


Using the general procedure, 3-chloroaniline (0.127 g, 1 mmol) gave 5-[(3-chlorophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **3.13** (0.273 g, 97%); mp

160-162 °C (from ethanol); (Found C, 55.7; H, 4.35; N, 4.8. $C_{13}H_{12}ClNO_4$ requires C, 55.4; H, 4.25; N 4.95%); δ_H 11.20 (1H, d, 3J 14.2), 8.59 (1H, d, 3J 14.2), 7.36 (1H, t, 3J 8.0), 7.27-7.21 (2H, m), 7.13 (1H, m) and 1.74 (6H, s); δ_C 165.34 (quat), 163.16

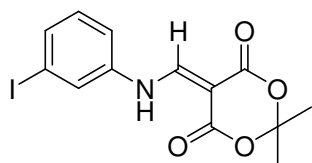
(quat), 152.28, 138.81 (quat), 131.04, 126.70, 118.11, 116.02, 105.31 (quat), 88.95 (quat) and 26.98 (2CH₃). One C not apparent; *m/z* 283 (M⁺, 6%), 281 (M⁺, 26), 225 (31), 223 (70), 180 (49), 178 (100), 153 (35), 151 (77), 113 (14) and 111 (39).

5-[(3-Bromophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **3.14**



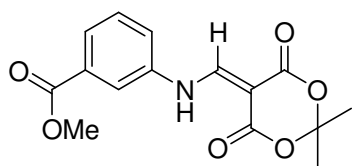
Using the general procedure, 3-bromoaniline (1.028 g, 5.98 mmol), gave 5-[(3-bromophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **3.14** (1.569 g, 80%); mp 163-164 °C (from ethanol). (Found C, 47.9; H, 3.5; N, 4.2. C₁₃H₁₂BrNO₄ requires C, 47.9; H, 3.7; N 4.3%). δ_H 11.15 (1H, d, ³*J* 14.2), 8.53 (1H, d, ³*J* 14.2), 7.40-7.10 (4H, m) and 1.68 (6H, s); δ_C 165.79 (quat), 163.99 (quat), 152.80, 139.46 (quat), 131.73, 130.73, 124.15 (quat), 121.51, 117.06, 105.76 (quat), 88.46 and 27.46 (2CH₃); *m/z* 327 (M⁺, 11%), 325 (M⁺, 11), 269 (33), 267 (33), 225 (40), 223 (49), 197 (98), 195 (100), 157 (84) and 155 (87).

5-[(3-Iodophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **3.15**



Using the general procedure, 3-iodoaniline (0.307 g, 1.4 mmol) gave 5-[(3-iodophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **3.15** (0.497 g, 95%) mp 157-158 °C (from ethanol); (Found C, 41.7; H, 3.25; N, 3.7. C₁₃H₁₂INO₄ requires C, 41.85; H, 3.25; N, 3.75%); δ_H 11.10 (1H, d, ³*J* 14.1), 8.52 (1H, d, ³*J* 14.1), 7.55 (2H, m), 7.12 (2H, m) and 1.69 (s, 6H); δ_C 165.81 (quat), 163.70 (quat), 152.75, 139.27 (quat), 136.11, 131.79, 127.22, 117.72, 105.77 (quat), 95.36 (quat), 88.40 (quat) and 27.47 (2CH₃); *m/z* 373 (M⁺, 79%), 315 (100), 270 (99), 203 (52) and 116 (93).

2,2-Dimethyl-5-[3-(methoxycarbonyl)phenylamino]-1,3-dioxane-1,6-dione **3.16**

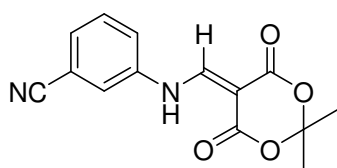


Using the general procedure, methyl 3-aminobenzoate (0.755 g, 5 mmol) gave 2,2-dimethyl-5-[3-(methoxycarbonyl)phenylamino]-1,3-dioxane-1,6-dione **3.16** (1.365 g, 90%); mp 158-159 °C (from ethanol);

(Found M^+ 305.08939, $C_{15}H_{15}NO_6$ requires 305.08986); δ_H 11.38 (1H, d, 3J 14.2), 8.78 (1H, d, 3J 4.2), 8.04-8.00 (2H, m), 7.64-7.50 (2H, m), 4.32 (3H, s) and 1.83 (6H, s); δ_C 166.08 (quat), 165.87 (quat), 163.74, 152.90, 138.43 (quat), 132.61 (quat), 130.64, 128.03, 122.65, 118.99, 105.73 (quat), 88.31 (quat), 52.94 (CH_3) and 27.44 ($2CH_3$); m/z 305 (M^+ , 24%), 247 (40), 203 (80), 202 (100), 175 (38) and 135 (23).

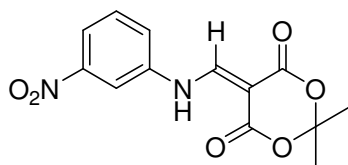
3-[(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-benzonitrile

3.17



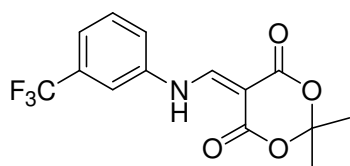
Using the general procedure, 3-aminobenzonitrile (0.295 g, 2.5 mmol) gave 3-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-benzonitrile **3.17** (0.638 g, 94%); mp 199-200 °C (from ethanol); (Found C, 61.75; H, 4.45; N, 10.30. $C_{14}H_{12}N_2O_4$ requires C, 61.45; H, 4.35; N, 10.20%); δ_H 11.23 (1H, d, 3J 14.0), 8.58 (1H, d, 3J 14.0), 7.55-7.43 (4H, m) and 1.70 (6H, s); δ_C 165.76 (quat), 163.45 (quat), 152.70, 139.21, 131.49, 130.29, 122.41, 121.77, 117.80 (quat), 114.78 (quat), 106.01 (quat), 89.27 (quat) and 27.51 ($2CH_3$); m/z 272 (M^+ , 37%), 214 (75) and 169 (100).

2,2-Dimethyl-5-[(3-nitrophenylamino)-methylene]-[1,3]dioxane-4,6-dione 3.18



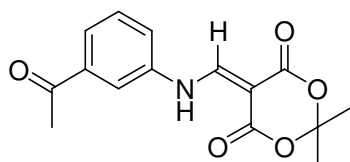
Using the general procedure, 3-nitroaniline (0.690g, 5 mmol), gave 2,2-dimethyl-5-[(3-nitrophenylamino)methylene]-[1,3]dioxane-4,6-dione **3.18** (1.423 g, 98%); mp 204-205 °C (from ethanol). (Found C, 53.45; H, 4.15; N, 9.6. $C_{13}H_{12}N_2O_6$ requires C, 53.25; H, 3.9; N, 9.50%); δ_H 11.32 (1H, d, 3J 13.9), 8.65 (1H, t, 3J 13.9), 8.10-8.04 (2H, m), 7.62-7.50 (2H, m) and 1.50 (6H, s); δ_C (d_6 -DMSO) 164.22 (quat), 163.40 (quat), 154.60, 148.72 (quat), 140.84 (quat), 131.13, 126.26, 120.79, 115.26, 104.62 (quat), 88.26 (quat) and 26.86 ($2CH_3$). m/z 292 (M^+ , 20%), 234 (100), 190 (4), 189 (10) and 132 (11).

2,2-Dimethyl-5-[(3-trifluoromethyl-phenylamino)-methylene]-[1,3]dioxane-4,6-dione 3.19



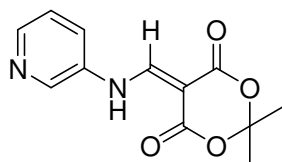
Using the general procedure, 3-(trifluoromethyl)aniline (3.22 g, 20 mmol) gave 2,2-dimethyl-5-[(3-trifluoromethyl-phenylamino)-methylene]-[1,3]dioxane-4,6-dione **3.19** as a yellow solid (5.93 g, 94%); mp 153 – 155 °C (from methanol, lit.,¹⁰ 155 – 156 °C); δ_H 11.33 (1H, d, 3J 14.1), 8.68 (1H, d, 3J 14.1), 7.62 -7.45 (4H, m) and 1.78 (6H, s); m/z 315 (M^+ , 22%), 257 (100), 213 (98), 185 (73) and 161 (83).

5-[(3-Acetylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.20**



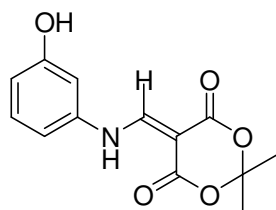
Using the general procedure, 3-aminoacetophenone (0.675 g, 5 mmol) gave 5-[(3-acetylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.20** as an orange solid (1.264 g, 87%); mp 156-157 °C (from ethanol); (Found M^+ 289.09481; $C_{15}H_{15}NO_5$ requires 289.09447) δ_H 11.31 (1H, d, 3J 14.2), 8.68 (1H, d, 3J 14.2), 7.86-7.82 (2H, m), 7.54 (1H, t, 3J 7.7), 7.43 (1H, m), 2.55, (3H, s) and 1.73 (6H, s); δ_C 197.01 (quat), 165.84 (quat), 163.68 (quat), 152.98, 139.16 (quat), 138.76 (quat), 130.85, 126.87, 122.58, 117.75, 105.70 (quat), 88.36 (quat), 27.43 (2CH₃) and 27.10 (CH₃); m/z 289 (M^+ , 53%), 231 (100), 186 (94), 159 (66) and 144 (78).

2,2-Dimethyl-5-(pyridin-3-ylaminomethylene)-[1,3]-dioxane-4,6-dione **3.21**



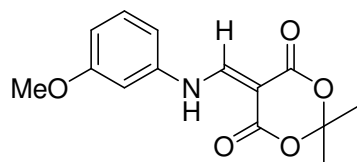
Using the general procedure, 3-aminopyridine (0.471 g, 5 mmol), gave 2,2-dimethyl-5-(pyridin-3-ylaminomethylene)-[1,3]-dioxane-4,6-dione **3.21** (1.192 g, 96%); mp 154-155 °C (from ethanol). (Found C, 58.0; H, 4.5; N, 11.2. $C_{12}H_{12}N_2O_6$ requires C, 58.3; H, 4.5; N, 11.3%). δ_H 11.20 (1H, d, 3J 13.9), 8.59 (2H, m), 8.47 (1H, dd, 3J 4.7, 4J 1.2), 7.59 (1H, d, 3J 8.3), 7.34 (1H, dd, 3J 8.3, 4J 4.7) and 1.69 (6H, s); δ_C 165.80 (quat), 163.49 (quat), 153.21, 148.20, 140.90, 135.01 (quat), 125.19, 124.69, 105.84 (quat), 89.09 (quat) and 27.47 (2CH₃). m/z 248 (M^+ , 41%), 190 (87), 146 (27), 145 (100), 118 (87) and 78 (59).

2,2-Dimethyl-5-[(3-hydroxyphenylamino)methylene]-1,3-dioxane-4,6-dione **3.22**



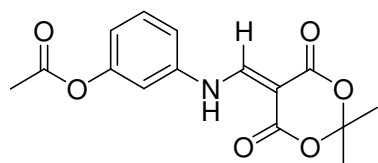
Using the general procedure, 3-aminophenol (0.550 g, 5 mmol) gave 2,2-dimethyl-5-[(3-hydroxyphenylamino)methylene]-[1,3]-dioxane-4,6-dione **3.22** as a yellow solid (1.103 g, 83%); mp 203-205 °C (from ethanol, lit.,³⁵ 208-210 °C). (Found C, 58.65; H, 4.7; N, 5.15. $C_{13}H_{13}NO_5 \cdot 0.2H_2O$ requires C, 58.5; H, 4.9; N, 5.25 %) δ_H (d_6 -DMSO) 10.87 (1H, br s), 9.64 (1H, br s), 8.26 (1H, s), 6.99 (1H, t, 3J 8.1), 6.73 (1H, d, 3J 7.9), 6.68 (1H, t, 4J 1.8), 6.45 (1H, dd, 3J 8.0, 4J 1.8) and 1.43 (6H, s); δ_C (d_6 -DMSO) 163.80 (2 quat), 158.76 (quat), 153.23, 139.90 (quat), 130.92, 113.87, 109.79, 106.08, 104.54 (quat), 88.82 (quat) and 26.81 (2CH₃). m/z 263 (M^+ , 51%), 205 (75), 161 (19), 160 (74), 133 (100) and 93 (9).

2,2-Dimethyl-5-[(3-methoxyphenylamino)-methylene]-[1,3]-dioxane-4,6-dione **3.23**



Using the general procedure, *m*-anisidine (1.353 g, 11 mmol) gave 5-[(3-methoxyphenylamino)-methylene]-2,2-dimethyl-[1,3]-dioxane-4,6-dione **3.23** (2.623 g, 86%) mp 112 – 113 °C (from ethanol). (Found C, 60.9; H, 5.45; N, 5.0. $C_{14}H_{15}NO_5$ requires C, 60.65; H, 5.40; N, 5.05 %) δ_H 11.18 (1H, d, 3J 14.3), 8.60 (1H, d, 3J 14.3), 7.29 (1H, m), 6.83-6.72 (3H, m), 3.81 (3H, s) and 1.72 (6H, s). δ_C 165.37 (quat), 163.42 (quat), 160.80 (quat), 152.39, 138.42 (quat), 130.79, 112.35, 110.00, 105.03 (quat), 103.63, 87.01 (quat), 55.39 (CH₃) and 26.85 (2CH₃); m/z 277 (M^+ , 49%), 219 (65), 175 (49), 174 (85), 147 (95), 132 (100) and 104 (48).

5-[(3-Acetoxyphenylamino)methylene]-2,2-dimethyl-[1,3]-dioxane-4,6-dione **3.24**



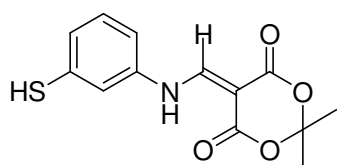
Using the general procedure, 3-acetoxyaniline (0.419 g, 2.5 mmol), gave 5-[(3-acetoxyphenylamino)methylene]-2,2-dimethyl-[1,3]-dioxane-4,6-dione **3.24** as a yellow solid (0.573 g, 75%); mp 172 – 174 °C

(from ethanol); (Found C., 58.9; H., 4.5; 4.3. C₁₅H₁₅NO₆ requires C., 59.0; H., 4.9; N., 4.6.); δ_H 11.16 (1H, d, 3J 14.1), 8.54 (1H, d, 3J 14.1), 7.37 (1H, t, 3J 8.1), 7.05 (1H, dd, 3J 8.1, 4J 2.2), 6.99 – 6.92 (2H, m), 2.26 (3H, s) and 1.68 (6H, s); δ_C 169.37 (quat), 165.83 (quat), 163.78 (quat), 152.87, 152.26 (quat), 139.17 (quat), 131.35, 120.29, 115.72, 112.06, 105.73 (quat), 88.15 (quat), 27.44 (2CH₃) and 21.42 (CH₃); m/z 305 (M⁺, 62 %), 247 (75), 205 (62), 187 (69) 177 (48) and 160 (100).

Alternative route to 5-[(3-Acetoxyphenylamino)methylene]-2,2-dimethyl-[1,3]-dioxane-4,6-dione **3.24**

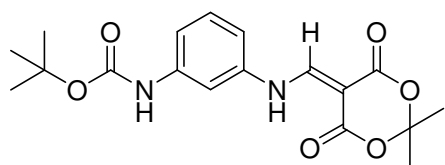
A solution of 2,2-dimethyl-5-[(3-hydroxyphenylamino)methylene]-[1,3]-dioxane-4,6-dione **3.22** (0.952 g) in DCM (10 cm³) was cooled to 0 °C and pyridine (0.5 cm³) was added, followed by acetyl chloride (0.313 g). The mixture was warmed to room temperature and stirred for 2 h. The mixture was washed with HCl (1M), washed with water, dried over MgSO₄ and the solvent removed under vacuum to give compound **3.24** as a yellow solid (1.031 g, 93%), spectral data as above.

2,2-Dimethyl-5-[(3-mercaptophenylamino)-methylene]-[1,3]dioxane-4,6-dione **3.25**



Using the general procedure, 3-aminothiophenol (1.25 g, 10 mmol) gave 2,2-dimethyl-5-[(3-mercaptophenylamino)methylene]-[1,3]dioxane-4,6-dione **3.25** as a yellow solid (2.46 g, 89%); mp 147-149 °C (from ethanol); (Found C, 55.95; H, 4.35; N, 4.85. C₁₃H₁₃NO₄S requires C, 55.9; H, 4.65; N, 5.0); δ_H 11.09 (1H, d, 3J 14.3), 8.53 (1H, d, 3J 14.3), 7.28 (1H, m), 7.09-7.06 (2H, m), 6.95 (1H, m), 3.79 (1H, s) and 1.75 (6H, s); δ_C 165.85 (quat), 163.80 (quat), 152.82, 138.77 (quat), 134.51 (quat), 130.97, 127.61, 118.54, 115.50, 105.69 (quat), 88.06 (quat) and 27.45 (2CH₃); m/z 279 (M⁺, 75%), 221 (84), 203 (52), 176 (84), 149 (100) and 125 (80).

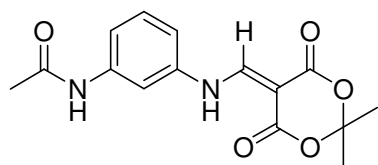
5-[3-(*tert*-Butoxycarbonylamino)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.26**



Using the general procedure, *tert*-butyl (3-aminophenyl)-carbamate (0.42 g, 2 mmol), gave 5-[3-(*tert*-butoxycarbonylamino)phenylamino]-2,2-dimethyl-[1,3]-dioxane-4,6-dione **3.26** (0.72

g, 99%); mp 184-185 °C (from ethanol); (Found C, 59.6; H, 6.2; N, 7.75. C₁₈H₂₂N₂O₆ requires C, 59.65; H, 6.1; N, 7.75%) δ_H 11.19 (1H, d, 3J 14.3), 8.63 (1H, d, 3J 14.3), 7.61 (1H, s), 7.31 (1H, t, 3J 8.0), 7.04 (1H, dd, 3J 8.0, 4J 1.4), 6.90 (1H, dd, 3J 8.0, 4J 1.4), 6.72 (1H, s), 1.72 (6H, s) and 1.52 (9H, s); δ_C 165.86 (quat), 163.92 (quat), 153.08, 152.80 (quat), 140.65 (quat), 138.94 (quat), 130.83, 116.75, 112.55, 108.39, 105.54 (quat), 87.67 (quat), 81.67 (quat), 28.64 (3CH₃) and 27.40 (2CH₃); m/z 362 (M⁺, 72 %), 306 (48), 262 (16), 248 (68) 231 (52), 204 (78), 186 (59), 132 (74) and 57 (100).

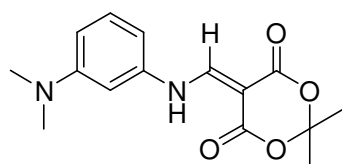
5-[3-(Acetamido)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.27**



Using the general procedure, 3-aminoacetamide (2.25 g, 15 mmol), gave 5-[3-(acetamido)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.27** (4.18 g, 92%); mp 200-201 °C (from ethanol); (Found C,

59.35; H, 4.95; N, 9.2. C₁₅H₁₆N₂O₅ requires C, 59.2; H, 5.25; N, 9.2%) δ_H 11.13 (1H, d, 3J 14.3), 8.53 (1H, d, 3J 14.3), 7.62 (2H, s), 7.28 (1H, t, 3J 8.0), 7.19 (1H, m), 6.89 (1H, d, 3J 7.8), 2.11 (3H, s) and 1.68 (6H, s); δ_C 169.04 (quat), 165.85 (quat), 163.99 (quat), 153.01, 140.15, 138.81, 130.94, 117.98, 113.75, 109.83, 105.66 (quat), 87.79 (quat), 27.45 (2CH₃) and 25.04 (CH₃); m/z 304 (M⁺, 53%), 246 (34), 228 (61), 186 (73), 160 (86), 132 (100) and 104 (29).

2,2-Dimethyl-5-[(3-dimethylaminophenylamino)-methylene]-[1,3]dioxane-4,6-dione **3.28**



A solution of *N,N*-dimethyl-*m*-phenylenediamine dihydrochloride (1.045 g, 5 mmol) in acetonitrile (75 ml) was treated with triethylamine (1.39 cm³, 10 mmol) and stirred at room temperature for 0.5 h. Methoxymethylene

Meldrum's acid (0.930 g, 5 mmol) was added and the mixture stirred for a further 2.5

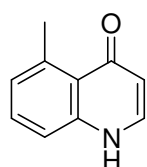
h. The solvent was removed to give a yellow solid. The yellow solid was dissolved in dichloromethane and treated with NaOH (1 M). The organic layer was extracted and the solvent removed to give 2,2-dimethyl-5-[(3-dimethylaminophenylamino)-methylene]-[1,3]dioxane-4,6-dione **3.28** (1.382 g, 95%); mp 151-152 °C (from ethanol); (Found C., 61.85; H., 6.05; N., 9.55. C₁₅H₁₉N₂O₄ requires C., 62.05; H., 6.2; N., 9.65.); δ_H 11.15 (1H, d, 3J 14.5), 8.57 (1H, d, 3J 14.5), 7.17 (1H, t, 3J 8.1), 6.54 - 6.47 (2H, m), 6.36 (1H, t, 4J 2.2), 2.92 (6H, s) and 1.68 (6H, s); δ_C 165.98 (quat), 164.12 (quat), 152.91, 151.94 (quat), 139.03 (quat), 130.91, 111.09, 105.64, 105.41 (quat), 101.78, 86.99 (quat), 40.76 (2CH₃) and 27.38 (2CH₃). m/z 290 (M⁺, 17%), 232 (11), 188 (11), 160 (54), 136 (100), 120 (15) and 84 (76).

Pyrolysis Experiments

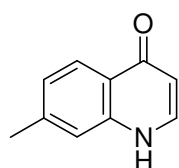
Analysis of the quinolinone regioisomers was carried out from the ¹H NMR spectrum of the mixture. Each resonance of the major regioisomer could usually be identified by the presence of a *meta*-coupled singlet (for the 7-substituted product) or a triplet (for the 5-substituted product), leading to unambiguous assignment of the regiochemistry. Where applicable, identifiable signals of the minor regioisomer are also quoted. Isomer ratios are quoted as ratios of 5-substituted:7-substituted.

Pyrolysis of 2,2-Dimethyl-5-(3-tolylaminomethylene)-[1,3]dioxane-4,6-dione **3.9**

Pyrolysis of compound **3.9** (500.3 mg, T_f 650 °C, T_i 180 °C, P 2.3 – 2.7 × 10⁻² Torr, 10 min) gave a mixture of 5-methyl-1*H*-quinolin-4-one **3.29** and 7-methyl-1*H*-quinolin-4-one **3.30** (0.27 g, 89%) in the ratio 26:74.



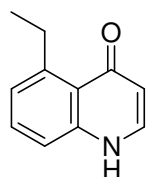
5-Methyl-1*H*-quinolin-4-one **3.29** δ_H (d_6 -DMSO) 7.85 (1H, d, 3J 7.3), 7.61 (1H, t, 3J 8.1), 7.51 (1H, m), 7.16 (1H, d, 3J 6.9), 6.14 (1H, d, 3J 7.4) and 2.99 (3H, s)



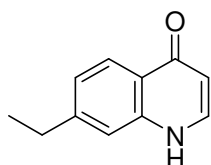
7-Methyl-1*H*-quinolin-4-one **3.30** δ_H (d_6 -DMSO) 11.85 (1H, s, NH), 8.17 (1H, d, 3J 8.2), 8.05 (1H, d, 3J 7.4), 7.49 (1H, d, 4J 0.6), 7.32 (1H, dd, 3J 8.2, 4J 0.6), 6.19 (1H, d, 3J 7.4) and 2.59 (3H, s)

Pyrolysis of 5-[(3-ethylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6 – dione 3.10

Pyrolysis of compound **3.10** (907 mg, T_f 600 °C, T_i 180 °C, P 1.1×10^{-2} Torr) gave a mixture of 5-ethyl-1*H*-quinolin-4-one **3.31** and 7-ethyl-1*H*-quinolin-4-one **3.32** (0.48 g, 84%) in a ratio of 11:89.

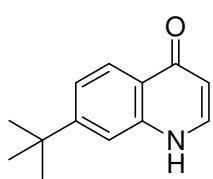


5-Ethyl-1*H*-quinolin-4-one **3.31** δ_H (d_6 -DMSO) 7.77 (1H, m), 7.47 (1H, t, 3J 8.3), 7.00 (1H, dd, 3J 7.1, 4J 1.4), 5.94 (1H, s), 2.76 (2H, q, 3J 7.2) and 1.13 (3H, t, 3J 7.2).



7-Ethyl-1*H*-quinolin-4-one **3.32** mp 152 °C (from acetonitrile), (Found C, 76.2; H, 6.25; N, 8.1. $C_{11}H_{11}NO$ requires C, 76.3; H, 6.4; N, 8.05 %) δ_H (d_6 -DMSO) 11.68 (1H, s), 7.98 (1H, d, 3J 8.3), 7.85 (1H, dd, 3J 7.4), 7.31 (1H, s), 7.17 (1H, dd, 3J 8.3, 4J 1.1), 5.98 (1H, d, 3J 7.4), 2.70 (2H, q, 3J 7.6) and 1.22 (3H, t, 3J 7.6). m/z 173 (M^+ , 100%), 158 (34), 145 (31), 130 (65) and 117 (25).

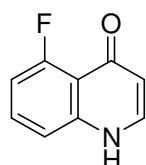
Pyrolysis of 5-[(3-*tert*-butylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane - 4,6-dione 3.11



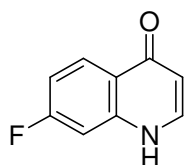
Pyrolysis of compound **3.11** (501 mg, T_f 650 °C, T_i 190 °C, P 3.2×10^{-2} Torr, t 6 min) gave 7-*tert*-butyl-1*H*-quinolin-4-one **3.33** (0.319 g, 96%); mp 199 – 201 °C (from acetonitrile); (Found C, 77.25; H, 7.45; N, 6.8. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.45; N 6.95%); δ_H (d_6 -DMSO) 11.71 (1H, s), 8.06 (1H, d, 3J 8.6), 7.92 (1H, t, 3J 7.2), 7.50 (1H, s), 7.42 (1H, dd, 3J 8.6), 6.04 (1H, d, 3J 7.2) and 1.34 (9H, s); δ_C 177.10 (quat), 154.89 (quat), 140.40 (quat), 139.58, 125.10, 124.11 (quat), 121.69, 114.17, 109.00, 35.12 (quat) and 31.07 (3CH₃); m/z 201 (M^+ , 44%), 186 (100), 134 (80), 83 (33) and 57 (32).

Pyrolysis of 2,2-Dimethyl-5-[(3-fluorophenylamino)-methylene]-1,3-dioxane -4,6-dione **3.12**

Pyrolysis of compound **3.12** (499.8 mg, T_f 650 °C, T_i 150 °C, P $2.4 - 2.7 \times 10^{-2}$ Torr, t 0.5 h) gave a mixture of 5-fluoro-1*H*-quinolin-4-one **3.34** and 7-fluoro-1*H*-quinolin-4-one **3.35** (0.26 g, 85%) in a ratio of 8:92



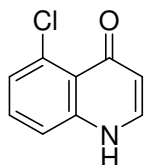
5-Fluoro-1*H*-quinolin-4-one **3.34** δ_H (d_6 -DMSO) 7.87 (1H, d, 3J 7.5), 7.59 (1H, m), 7.37 (1H, s), 6.99 (1H, dd, $^3J_{HF}$ 11.2, $^3J_{HH}$ 7.9) and 6.01 (1H, d, 3J 7.4)



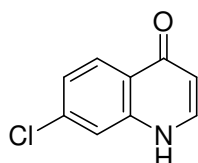
7-Fluoro-1*H*-quinolin-4-one **3.35** δ_H (d_6 -DMSO) 11.83 (1H, br s), 8.17 (1H, dd, 3J 9.0, 4J 6.5), 7.95 (1H, d, 3J 7.5), 7.31 (1H, dd, 3J 10.2, 4J 2.5), 7.19 (1H, td, $^3J_{HF} = 3J_{HH}$ 8.9, 4J 2.5), 6.40 (1H, d, 3J 7.5); δ_C (d_6 -DMSO) 176.43 (quat), 163.87 (quat, 2J 248.2), 141.50 (quat, 4J 6.3), 140.1, 128.41 (4J 10.7), 122.95 (quat), 112.02 (3J 23.4), 109.13 and 103.46 (3J 24.9)

Pyrolysis of 5-[(3-chlorophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **3.13**

Pyrolysis of compound **3.13** (793 mg, T_f 600 °C, T_i 180 °C, P 6.0×10^{-2} Torr) gave a mixture of 5-chloro-1*H*-quinolin-4-one **3.36** and 7-chloro-1*H*-quinolin-4-one **3.37** (0.40 g, 78 %) in a ratio of 22:78.



5-Chloro-1*H*-quinolin-4-one **3.36** δ_H (d_6 -DMSO) 7.82 (1H, t, 3J 5.9), 7.44 (2H, m), 7.25 (1H, dd, 3J 7.1, 4J 1.8) and 6.00 (1H, dd, 3J 7.4, 4J 1.3)



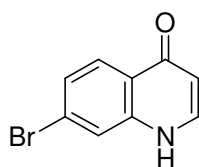
7-Chloro-1*H*-quinolin-4-one **3.37** δ_H (d_6 -DMSO) 8.09 (1H, d, 3J 8.7), 7.95 (1H, d, 3J 7.5), 7.60 (1H, d, 3J 2.0), 7.35 (1H, dd, 3J 8.7, 4J 2.0) and 6.07 (1H, d, 3J 7.5); δ_C 176.42 (quat), 140.87 (quat), 140.07, 136.32 (quat), 127.43, 124.47 (quat), 123.57, 117.50 and 109.41; m/z 181 (M^+ , 55%), 179 (M^+ , 100), 153 (36), 151 (61), 117 (19) and 115 (34).

Pyrolysis of 5-[(3-bromophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **3.14**

Pyrolysis of compound **3.14** (499.9 mg, T_f 650 °C, T_i 180 °C, P $2.5 - 3.0 \times 10^{-2}$ Torr, t 13 min) gave a mixture of 5-bromo-1*H*-quinolin-4-one **3.38** and 7-bromo-1*H*-quinolin-4-one **3.39** (0.166 g, 48%) in a ratio of 25:75.



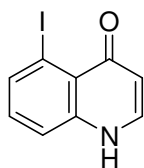
5-Bromo-1*H*-quinolin-4-one **3.38** δ_H (d_6 -DMSO) 7.57 (1H, m) 7.34 (1H, dd, 3J 7.7, 4J 1.7) and 5.85 (1H, d 3J 7.5)



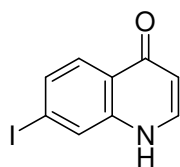
7-Bromo-1*H*-quinolin-4-one **3.39** δ_H (d_6 -DMSO) 11.62 (1H, s), 7.82 (1H, d, 3J 8.7), 7.76 (1H, d, 3J 7.5), 7.57 (1H, d, 4J 2.1), 7.28 (1H, d, 4J 2.1) and 5.88 (1H, d, 3J 7.5).

Pyrolysis of 5-[(3-iodophenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione

Pyrolysis of compound **3.15** (299.7 mg, T_f 650 °C, T_i 190 °C, P $2.6 - 2.8 \times 10^{-2}$ Torr, t 15 min) gave a mixture of 5-iodo-1*H*-quinolin-4-one **3.40** and 7-iodo-1*H*-quinolin-4-one **3.41** (0.17 g, 77%) in a ratio of 15:85.



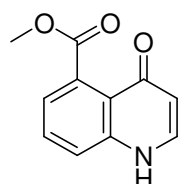
5-Iodo-1*H*-quinolin-4-one **3.40** δ_H (d_6 -DMSO) 8.01 (2H, m), 7.58 (1H, dd, 3J 8.3, 4J 1.1), 7.30 (1H, t, 3J 7.7) and 6.11 (1H, d, 3J 7.4)



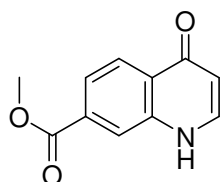
7-Iodo-1*H*-quinolin-4-one **3.41** δ_H (d_6 -DMSO) 11.87 (1H, s), 8.01 (2H, m), 7.88 (1H, d, 3J 8.5), 7.69 (1H, dd, 3J 8.5, 4J 1.4) and 6.13 (1H, d, 3J 7.4)

Pyrolysis of 2,2-Dimethyl-5-[3-(methoxycarbonyl)phenylamino]-1,3-dioxane -1,6-dione **3.16**

Pyrolysis of compound **3.16** (299.6 mg, T_f 650 °C, T_i 190 °C, P $2.5 - 3.2 \times 10^{-2}$ Torr, t 10 min) gave a mixture of 5-methoxycarbonylquinolin-4-one **3.42** and 7-methoxycarbonylquinolin-4-one **3.43** (0.151 g, 80%) in the ratio of 18.82.



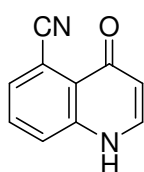
5-methoxycarbonylquinolin-4-one **3.42** δ_H (d_6 -DMSO) 8.07 (1H, d, 3J 7.4), 7.75 (2H, m), 7.26 (1H, dd, 3J 6.4, 4J 1.8), 6.09 (1H, d, 3J 7.4) and 3.83 (3H, s)



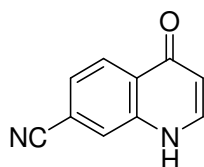
7-methoxycarbonylquinolin-4-one **3.43** δ_H (d_6 -DMSO) 8.24 – 8.20 (2H, m), 8.04 (1H, d, 3J 7.5), 7.85 (1H, dd, 3J 8.5, 4J 1.1), 6.18 (1H, d, 3J 7.5) and 3.96 (3H, s)

Pyrolysis of 3-[(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-benzonitrile **3.17**

Pyrolysis of compound **3.17** (300.6 mg, T_f 650 °C, T_i 210 °C, P 3.0×10^{-2} Torr, t 25 min) gave a mixture of 5-cyano-1H-quinolin-4-one **3.44** and 7-cyano-1H-quinolin-4-one **3.45** (0.176 g, 94%) in the ratio of 25:75.



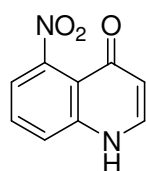
5-Cyano-1H-quinolin-4-one **3.44** δ_H (d_6 -DMSO) 7.87 (1H, d, 3J 2.5), 7.85 (1H, t, 3J 2.5) and 6.20 (1H, d, 3J 7.5)



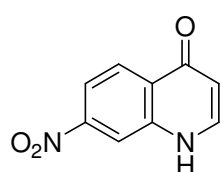
7-Cyano-1H-quinolin-4-one **3.45** δ_H (d_6 -DMSO) 8.28 (1H, d, 3J 8.3), 8.06 (1H, m), 7.81 (1H, m), 7.71 (1H, dd, 3J 8.3, 4J 1.5) and 6.21 (1H, d, 3J 7.5).

Pyrolysis of 2,2-Dimethyl-5-[(3-nitrophenylamino)-methylene]-[1,3]dioxane-4,6 – dione

Pyrolysis of compound **3.18** (299.8 mg, T_f 650 °C, T_i 200 °C, P 2.5 - 3.0 × 10⁻² Torr, t 40 min) gave a mixture of 5-nitro-1*H*-quinolin-4-one **3.46** and 7-nitro-1*H*-quinolin-4-one **3.47** (0.110 g, 56 %) in the ratio of 17:83.

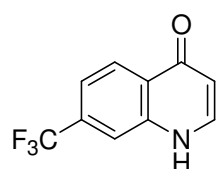


5-Nitro-1*H*-quinolin-4-one **3.46** δ_H (d_6 -DMSO) 7.58 (1H, m), 7.19 (1H, m), 7.10 (1H, m) and 7.86 (1H, d, 3J 7.3)



7-Nitro-1*H*-quinolin-4-one **3.47** δ_H (d_6 -DMSO) 11.60 (1H, s), 8.25 (1H, d, 3J 1.7), 8.10 (1H, d, 3J 8.9), 7.93 (1H, d, 3J 7.5), 7.85 (1H, dd, 3J 8.9, 4J 1.7) and 6.00 (1H, d, 3J 7.4)

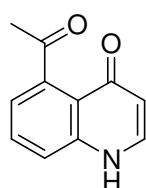
Pyrolysis of 2,2-dimethyl-5-[(3-trifluoromethyl-phenylamino)-methylene]-[1,3]dioxane-4,6-dione **3.19**



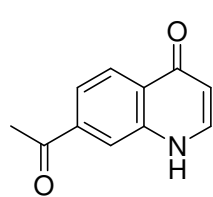
Pyrolysis of compound **3.19** (w 1.208 g, T_f 600 °C, T_i 160 °C, P 2.1 - 2.3 × 10⁻² Torr, t 50 min) gave 7-(trifluoromethyl)quinolin-4-one **3.48** as a pale yellow solid (0.821 g, 99%); mp 262 – 263 °C (from ethanol); δ_H 11.98 (1H, s, br), 8.27 (1H, d, 3J 8.7), 8.04 (1H, d, 3J 7.4), 7.90 (1H, s), 7.58 (1H, dd, 3J 8.7, 4J 1.5) and 6.15 (1H, d, 3J 7.4).

Pyrolysis of 5-[(3-acetylphenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane -4,6-dione **3.20**

Pyrolysis of compound **3.20** (300.8 mg, T_f 500 °C, T_i 240 °C, P 2.2 – 2.4 × 10⁻² Torr, t 11 min) gave a mixture of 5-acetyl-1*H*-quinolin-4-one **3.49** and 7-acetyl-1*H*-quinolin-4-one **3.50** (0.135 g, 69%) in the ratio of 52:48.



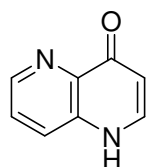
5-Acetyl-1*H*-quinolin-4-one **3.49** δ_H (d_6 -DMSO) 12.07 (1H, br s), 8.03 (1H, m), 7.87 (1H, dd, 3J 8.5, 4J 1.4), 7.69 (1H, m), 7.08 (1H, dd, 3J 7.1, 4J 1.4), 6.14 (1H, dd, 3J 7.1, 4J 1.4) and 2.40 (3H, s)



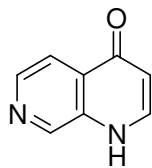
7-Acetyl-1H-quinolin-4-one **3.50** δ_H (d_6 -DMSO) 8.22 (1H, d, 3J 8.5), 8.17 (1H, d, 3J 1.3), 8.09 (1H, dd, 3J 6.1, 4J 5.9), 7.73 (1H, d, 3J 6.9), 7.65 (1H, dd, 3J 7.0, 4J 1.4), 6.17 (1H, d, 3J 7.3) and 2.71 (3H, s)

Pyrolysis of 2,2-Dimethyl-5-(pyridin-3-ylaminomethylene)-1,3-dioxane-4,6-dione **3.21**

Pyrolysis of compound **3.21** (300.0 mg, T_f 650 °C, T_i 190 °C, P $2.2 - 2.6 \times 10^{-2}$ Torr, t 13 min) gave a mixture of 1H-[1,5]naphthyridin-4-one **3.51** and 1H-[1,7]naphthyridin-4-one **3.52** (0.163 g, 92 %) in the ratio of 13:87.

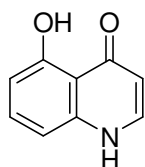


1H-[1,5]Naphthyridin-4-one **3.51** δ_H (d_6 -DMSO) 8.87 (1H, m), 8.21 (2H, m), 7.90 (1H, dd, 3J 8.5, 4J 4.2) and 6.48 (1H, d, 3J 7.2)



1H-[1,7]Naphthyridin-4-one **3.52** δ_H (d_6 -DMSO) 9.22 (1H, s), 8.65 (1H, d, 3J 5.3), 8.27 (1H, d, 3J 7.4), 8.12 (1H, dd, 3J 5.3) and 6.38 (1H, d, 3J 7.4).

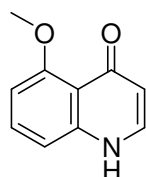
Pyrolysis of 2,2-Dimethyl-5-[(3-hydroxyphenylamino)methylene]-1,3-dioxane-4,6-dione



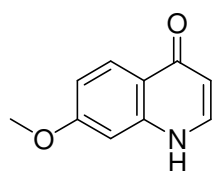
Pyrolysis of compound **3.22** (0.500 g, T_f 850 °C, T_i 170 °C, P $3.2 - 3.4 \times 10^{-2}$ Torr, t 0.5 h) gave 5-hydroxyquinolinone **3.53** as a pale yellow solid (0.167 g, 55%); mp 209 - 213 °C (from methanol, lit.,⁵⁵ 210- 215 °C) δ_H (d_6 -DMSO) 14.54 (1H, s), 12.25 (1H, s, br), 7.99 (1H, t, 3J 7.1), 7.48 (1H, t, 3J 8.3), 6.92 (1H, dd, 3J 8.3, 4J 0.8), 6.55 (1H, d, 3J 8.3) and 6.09 (1H, d, 3J 7.1); m/z 161 (M^+ , 62%), 159 (44), 151 (14), 144 (38), 133 (38) and 109 (100).

Pyrolysis of 5-[(3-Methoxyphenylamino)-methylene]-2,2-dimethyl-[1,3] dioxane-4,6-dione 3.23

Pyrolysis of compound **3.23** (1.500 g, T_f 600 °C, T_i 170 °C, P 2.6×10^{-2} Torr, t 22 min) gave a mixture of 5-methoxy-1*H*-quinolin-4-one **3.54** and 7-methoxy-1*H*-quinolin-4-one **3.55** (0.860 g, 91%) in a ratio of 10:90.

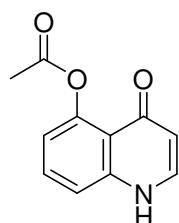


5-Methoxy-1*H*-quinolin-4-one **3.54** δ_H (d_6 -DMSO) 7.72 (1H, t, 3J 8.2), 6.80 (1H, d, 3J 8.0), 6.35 (1H, d, 3J 7.6) and 3.42 (3H, s).



7-Methoxy-1*H*-quinolin-4-one **3.55**; mp 212 – 214 °C (from methanol) (lit.,²⁷ 215 °C); δ_H (d_6 -DMSO) 11.85 (1H, s), 8.23 (1H, d, 3J 10.0), 8.05 (1H, m), 7.17 (1H, s), 6.20 (1H, d, 3J 7.4) and 4.08 (3H, s); δ_C (d_6 -DMSO) 177.39 (quat), 162.68 (quat), 142.69 (quat), 139.98, 127.69, 121.08 (quat), 114.08, 109.48, 99.96 and 56.31 (CH₃).

Pyrolysis of 5-[(3-Acetoxyphenylamino)methylene]-2,2-dimethyl-1,3-dioxane - 4,6-dione 3.24

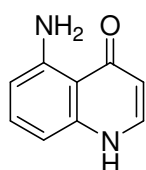


Pyrolysis of compound **3.24** (160.3 mg, T_f 500 °C, T_i 240 °C, P $2.5 - 2.9 \times 10^{-2}$ Torr, t min) gave 5-acetoxy-1*H*-quinolin-4-one **3.56** (105.6 mg, 99%); mp 182 – 184 °C (from acetonitrile); (Found C, 65.25; H, 4.5; N, 7.3. C₁₁H₉NO₃ requires C, 65.0; H, 4.45; N, 6.9%); δ_H (d_6 -DMSO) 11.89 (1H, s), 7.88 (1H, t, 3J 7.5), 7.65 (1H, t, 3J 8.5), 7.47 (1H, dd, 3J 8.5, 4J 1.1), 6.93 (1H, dd, 3J 7.5, 4J 1.1), 5.97 (1H, d, 3J 7.5) and 2.31 (3H, s); δ_C (d_6 -DMSO) 176.52 (quat), 169.46 (quat), 149.56 (quat), 142.39 (quat), 138.90, 132.02, 118.69 (quat), 116.70, 116.59, 110.85 and 21.50 (CH₃); m/z 203 (M⁺, 11%), 162 (15), 161 (100), 133 (22) and 104 (7).

Pyrolysis of 2,2-Dimethyl-5-[(3-mercaptophenylamino)methylene]-1,3-dioxane-4,6-dione 3.25

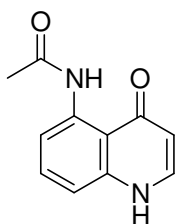
Pyrolysis of compound **3.25** (102.2 mg, T_f 600 °C, T_i 220 °C, P $2.3 - 2.4 \times 10^{-2}$ Torr, t 15 min) gave a complex mixture with no identifiable products by ^1H NMR spectroscopy

Pyrolysis of 5-[3-(*tert*-butoxycarbonylamino)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione 3.26



Pyrolysis of compound **3.26** (304.6 mg, T_f 600 °C, T_i 200 °C, P $2.2 - 2.6 \times 10^{-2}$ Torr, t 12 min) gave 5-amino-1*H*-quinolin-4-one **3.57** (0.0593 g, 44%); δ_H (d_6 -DMSO) 11.45 (1H, s), 7.57 (1H, t, 3J 7.1), 7.10 (1H, t, 3J 8.0), 6.38 (1H, d, 3J 8.0), 6.19 (1H, d, 3J 8.0) and 5.77 (1H, d, 3J 7.1); δ_C (d_6 -DMSO) 181.63 (quat), 151.30 (quat), 142.69 (quat), 138.46, 132.58, 112.27 (quat), 109.09, 106.32 and 102.53.

Pyrolysis of 5-[3-(acetamido)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione 3.27



Pyrolysis of compound **3.27** (300.8 mg, T_f 500 °C, T_i 240 °C, P $2.3 - 2.9 \times 10^{-2}$ Torr, t 16 min) gave 5-acetamido-1*H*-quinolin-4-one **3.58** (87.3 mg, 44%); mp 222 – 224 °C; (Found M^+ 202.07373, $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2$ requires 202.07368); δ_H (d_6 -DMSO) 13.77 (1H, s), 8.31 (1H, d, 3J 8.2), 7.88 (1H, m), 7.50 (1H, t, 3J 8.2), 7.12 (1H, d, 3J 8.2), 6.05 (1H, dd, 3J 7.2, 4J 1.1) and 2.00 (3H, s); δ_C (d_6 -DMSO) 181.19 (quat), 168.79 (quat), 141.48 (quat), 140.94 (quat), 139.72, 132.89, 113.54 (quat), 112.11, 111.43, 109.95 and 25.59 (CH_3); m/z 202 (M^+ , 5%) 160 (14), 150 (83) and 108 (100).

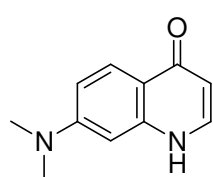
Temperature Profile for the Pyrolysis of 5-[3-(acetamido)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.27**

The inlet temperature was set at 240 °C for these reactions. Results are shown in table **3.6** below:

T_f /°C	wt /mg	P / $\times 10^{-2}$ Torr	t /min	3.58 /%	3.57 /%
500	100.9	2.5 – 2.9	13	100	0
600	100.9	2.3	7	97	3
700	101.6	2.5 – 2.8	13	80	20
800	100.4	2.6 – 2.9	5	62	38
900	100.2	3.4 – 4.4	9	37	67

Table 3.7 Results and conditions for the pyrolysis of compound **3.27**

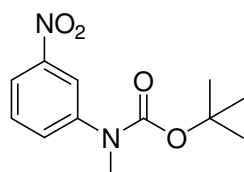
Pyrolysis of 5-[(3-Dimethylaminophenylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.28**



Pyrolysis of compound **3.28** (500.4 mg, T_f 650 °C, T_i 150 °C, P 2.6 – 3.2×10^{-2} Torr, t 50 min) gave 7-dimethylamino-1H-quinolin-4-one **3.59** (0.174 g, 54%); mp 265 – 267 °C (from acetonitrile). (Found C, 70.0; H, 6.35; N, 15.2. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.4; N, 14.9 %); δ_H (d_6 -DMSO) 11.25 (1H, s), 7.80 (1H, d, 3J 9.1), 7.62 (1H, d, 3J 7.4), 6.75 (1H, dd, 3J 9.1, 4J 2.5), 6.41 (1H, d, 3J 2.5), 5.77 (1H, d, 3J 7.4) and 2.93 (6H, s); δ_C 176.87 (quat), 152.59 (quat), 142.32 (quat), 138.76, 126.39, 117.10 (quat), 110.83, 108.14, 96.54 and 40.07 (2CH₃); m/z 188 (M^+ , 27%), 136 (100), 135 (87), 121 (18) and 93 (34).

Further Example of 5-Selective NH Cyclisation

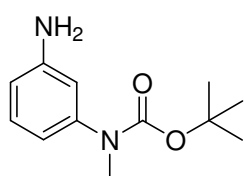
tert-Butyl *N*-methyl-(3-nitrophenyl)-carbamate⁵⁶ **3.62**



A solution of *tert*-butyl(3-nitrophenyl)-carbamate (1.19 g, 5 mmol) in DMF (10 cm³) was added to sodium hydride (241 mg, 10 mmol) and allowed to stir for 1 h. The reaction mixture was

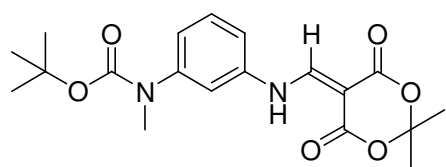
cooled to 0 °C, iodomethane (0.5 cm³, *ca.* 8 mmol) added and allowed to stir overnight at room temperature. Water (150 cm³) was added and extracted with EtOAc (2 × 50 cm³). The combined extracts were washed with brine, the organic layer dried over MgSO₄ and removal of the solvent gave a yellow oil (1.14 g, 91%); δ_H 8.16 (1H, d, ³*J* 2.2), 8.00 (1H, ddd, ³*J* 8.1, ⁴*J* 2.2, ⁵*J* 1.1), 7.61 (1H, ddd, ³*J* 8.1, ⁴*J* 2.2, ⁵*J* 1.1), 7.48 (1H, t, ³*J* 8.1), 3.31 (3H, s) and 1.49 (9H, s); δ_C 154.37 (quat), 148.64 (quat), 145.18 (quat), 131.22, 129.48, 120.19, 120.07, 81.89 (quat), 37.24 (CH₃) and 28.60 (3CH₃).

***tert*-Butyl *N*-methyl-(3-aminophenyl)-carbamate⁵⁶ 3.63**



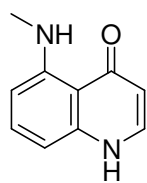
A solution of *tert*-butyl *N*-methyl-(3-nitrophenyl)-carbamate (0.63 g, 2.5 mmol) in EtOH (20 cm³) was hydrogenated at 5 bar for 2 h, using Pd/C (50 mg). The solution was filtered through celite and the solvent was removed to give an off-white solid (0.58 g, 100%); δ_H 7.12 (1H, t, ³*J* 7.9), 6.62 – 6.58 (2H, m), 6.32 (1H, ddd, ³*J* 8.0, ⁴*J* 2.3, ⁵*J* 0.9), 3.12 (3H, s) and 1.45 (9H, s); δ_C 155.21 (quat), 147.10 (quat), 145.19 (quat), 129.66, 116.17, 112.89, 112.78, 80.47 (quat), 37.73 (CH₃) and 28.73 (3CH₃).

5-[3-(*N*-methyl-*tert*-butoxycarbonylamino)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione 3.60



Using the general procedure, *tert*-butyl-*N*-methyl-(3-aminophenyl)-carbamate (0.58 g, 2.5 mmol) gave 5-[3-(*N*-methyl *tert*-butoxycarbonyl amino)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.60** (0.90 g, 96%); mp 184-185 °C (from ethanol); (Found C, 60.4; H, 6.5; N, 7.45. C₁₉H₂₄N₂O₆ requires C, 60.65; H, 6.4; N, 7.45%); δ_H 11.22 (1H, d, ³*J* 14.3), 8.62 (1H, d, ³*J* 14.3) 7.38 (1H, t, ³*J* 8.1), 7.23, (1H, m), 7.18 (1H, m), 7.06 (1H, dd, ³*J* 7.6, ⁴*J* 2.2), 3.28 (3H, s), 1.76 (6H, s) and 1.48 (9H, s); δ_C 165.88 (quat), 163.83 (quat), 154.63 (quat), 153.00, 145.93 (quat), 138.42 (quat), 130.48, 123.67, 115.56, 114.92, 105.59 (quat), 87.78 (quat), 81.47 (quat), 37.51 (CH₃), 28.67 (3CH₃) and 27.42 (2CH₃); *m/z* 376 (M⁺, 48%), 320 (48), 276 (29), 262 (31), 245 (17), 218 (100), 200 (56) and 146 (65).

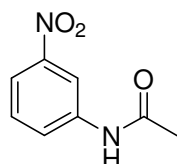
Pyrolysis of 5-[3-(*N*-methyl *tert*-butoxycarbonylamino)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione **3.60**



Pyrolysis of compound **3.60** (100.4 mg, T_f 600 °C, T_i 240 °C, P $2.4 - 2.6 \times 10^{-2}$ Torr, t 6 min) gave 5-(*N*-methylamino)-1*H*-quinolin-4-one **3.61** (31.0 mg, 67%); mp 121 – 123 °C; (Found M^+ 174.07864, $C_{10}H_{10}N_2O$ requires 174.07876) δ_H (d_6 -DMSO) 11.35 (1H, br s,), 9.58 (1H, q, 3J 5.1) 7.60 (1H, m), 7.23 (1H, t, 3J 8.1), 6.43 (1H, dd, 3J 8.1, 4J 1.0), 6.07 (1H, d, 3J 8.1), 5.81 (1H, dd, 3J 7.3, 4J 1.4) and 2.68 (3H, d, 3J 5.1); δ_C (d_6 -DMSO) 181.49 (quat), 151.74 (quat), 142.70 (quat), 138.27, 133.24, 112.04 (quat), 109.52, 102.50, 100.50 and 29.35 (CH_3); m/z 174 (M^+ , 100), 173 (41), 147 (56), 128 (38), 123 (24) and 117 (21).

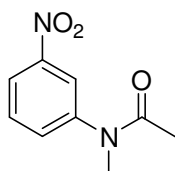
Further Examples of *N*-Acetyl Cyclisations

3-Nitroacetanilide⁵⁷ **3.67**



Acetyl chloride (6.25 g, 79.6 mmol) and pyridine (10 cm³) were added dropwise to a solution of *m*-nitroaniline (10.00 g, 72.4 mmol) in dichloromethane (100 cm³) at 0 °C. The reaction mixture was then stirred for 2 h, washed with 2N HCl, then with brine and the organic layer was dried over $MgSO_4$. The solvent was removed to give 3-nitroacetanilide as a fine yellow powder (10.52 g, 75%); mp 153-154 °C (lit.,⁵⁸ 155 °C); δ_H 10.48 (1H, s), 8.65 (1H, t, 4J 2.2), 7.93 – 7.88 (2H, m), 7.62 (1H, t, 3J 8.4) and 2.13 (3H, s); δ_C 169.48 (quat), 148.27 (quat), 140.69 (quat), 130.44, 125.21, 117.88, 113.32 and 24.36 (CH_3).

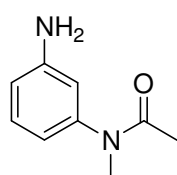
N*-Methyl-3-nitroacetanilide⁵⁷ **3.68*



A solution of 3-nitroacetanilide (2.26 g, 12.5 mmol) in dry THF (40 cm³) was added to sodium hydride (0.75 g, 18.8 mmol) at 0 °C. The reaction mixture was stirred for 10 min and iodomethane (1.2 cm³,

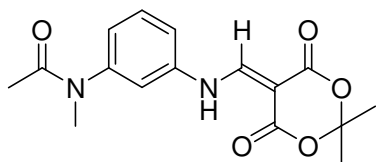
ca. 19.3 mmol) was added. The mixture was then stirred overnight. Removal of the solvent gave the crude product (1.83 g) and recrystallisation from EtOAc/n-hexane gave *N*-methyl-3-nitroacetanilide (0.69 g, 28%); mp 96-97 °C (from EtOAc/n-hexane, lit.⁵⁵ 95-96 °C); δ_H 8.25 (1H, m), 8.14 (1H, s), 7.70 – 7.60 (2H, m), 3.37 (3H, s) and 1.99 (3H, br s).

***N*-Methyl-3-aminoacetanilide⁵⁷ 3.69**



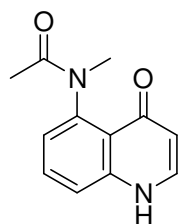
A solution of *N*-methyl-3-nitroacetanilide (0.49 g, 2.5 mmol) in ethyl acetate/ethanol (24 cm³, 1:1) was hydrogenated using Pd/C (50 mg) at 5 bar for 1 h to give *N*-methyl-3-aminoacetanilide as an orange oil (0.41 g, 100%); bp 105 – 106 °C (1 Torr); δ_H 7.11 (1H, m), 6.59 (1H, d, ³*J* 13.1) 6.45 (2H, m), 3.96 (2H, s, br), 3.18 (3H, s) and 1.85 (3H, s); δ_C 170.97 (quat), 148.45 (quat), 145.83 (quat), 130.71, 116.79, 114.55, 113.52, 37.31 (CH₃) and 22.60 (CH₃). NMR data matches literature data.⁵⁵

5-[3-(*N*-methylacetamido)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione 3.64



Using the general procedure, *N*-methyl-3-aminoacetamide (0.33 g, 2 mmol) gave 5-[3-(*N*-methylacetamido)phenylamino]-2,2-dimethyl-[1,3]-dioxane-4,6-dione **3.64** (0.60 g, 94%); mp 192-193 °C (from ethanol); (Found M^+ 318.12136, C₁₆H₁₈N₂O₅ requires 318.12102) δ_H 11.26 (1H, d, ³*J* 14.2), 8.63 (1H, d, ³*J* 14.2), 7.49 (1H, t, ³*J* 8.0), 7.24 (1H, d, ³*J* 8.1), 7.15 – 7.10 (2H, m), 3.38 (3H, s), 1.92 (3H, s, br) and 1.75 (6H, s); δ_C (90 MHz) 169.96 (quat), 165.31 (quat), 163.15 (quat), 152.29 (2CH), 146.17 (quat), 138.98 (quat), 131.24, 125.17, 116.71, 105.26 (quat), 87.90 (quat), 37.09 (CH₃), 26.93 (2CH₃) and 22.29 (CH₃); *m/z* 318 (M^+ , 73%), 260 (58), 218 (48), 200 (100), 188 (28), 173 (64) and 146 (95).

Pyrolysis of 5-[3-(*N*-Methylacetamido)phenylamino]-2,2-dimethyl-[1,3]dioxane-4,6-dione



Pyrolysis of compound **3.64** (100.6 mg, T_f 500 °C, T_i 240 °C, P 2.3 – 2.5×10^{-2} Torr, t 7 min) gave 5-(*N*-methylacetamido)-1*H*-quinolin-4-one **3.65** (45.4 mg, 66%); mp 249 – 251 °C; (Found M^+ 216.08964, $C_{12}H_{12}N_2O_2$ requires 216.08933); δ_H (d_6 -DMSO) 11.79 (1H, br s), 7.80 (1H, m), 7.63 (1H, t, 3J 7.3), 7.52 (1H, m), 7.06 (1H, dd, 3J 7.3, 4J 1.3), 2.94 (3H, s) and 1.47 (3H, s); δ_C (d_6 -DMSO) 176.42 (quat), 168.41 (quat), 142.50 (quat), 142.28 (quat), 138.30, 131.83, 123.93, 121.38 (quat), 118.96, 110.81, 36.30 (CH_3) and 21.95 (CH_3); m/z 216 (M^+ , 32%), 174 (100), 146 (18) and 117 (14).

Chapter 4

Synthesis of

8-Hydroxyquinolizinones by FVP

4.1 Introduction

4.1.1 Synthesis of Quinolizinones

Quinolizinones are a rare heterocyclic ring system, with 2 six-membered rings joined by a bridgehead nitrogen atom. There are only 259 reports of quinolizinones in the literature, a quarter of which are patents. The numbering system of the ring system is shown below (Figure 4.1)

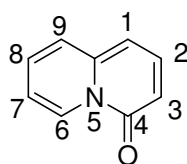
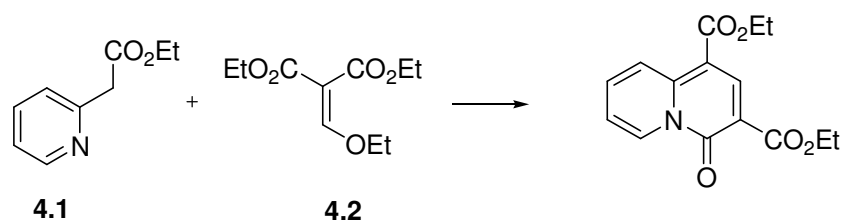


Figure 4.1 Structure of quinolizinone ring system

A comprehensive review of the synthesis of quinolizinones up to 1982 has been published,⁵⁹ covering a wide range of derivatives and properties of the compounds. This introduction aims to update the synthesis of quinolizinones after that date with representative examples. Typically the bond forming process is between the carbonyl carbon and pyridine nitrogen, so the first part of this review covers methodology that forms this bond to give quinolizinones based on the cyclisation precursor, followed by other synthetic methods.

The most common route to quinolizinones involves the use of activated α -picolines, which have been comprehensively covered in a review in this field.⁵⁹ Typically, pyridyl acetic esters **4.1** are used along with an active methylene compound, such as diethyl ethoxymethylene malonate **4.2** (Scheme 4.1)



Scheme 4.1 A representative synthesis of quinolizinones from pyridyl acetic ester **4.1**

Activated α -picolines have been used in the synthesis of quinolizinones as an alternative for quinolinones as antibacterial agents. One example⁶⁰ involved the synthesis of quinolizinones that are similar in structure to ciprofloxacin, a market quinolinone (Figure 4.2)

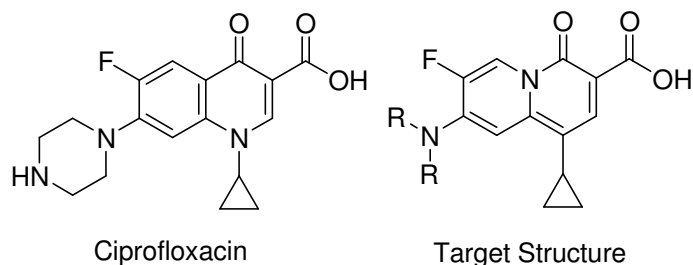
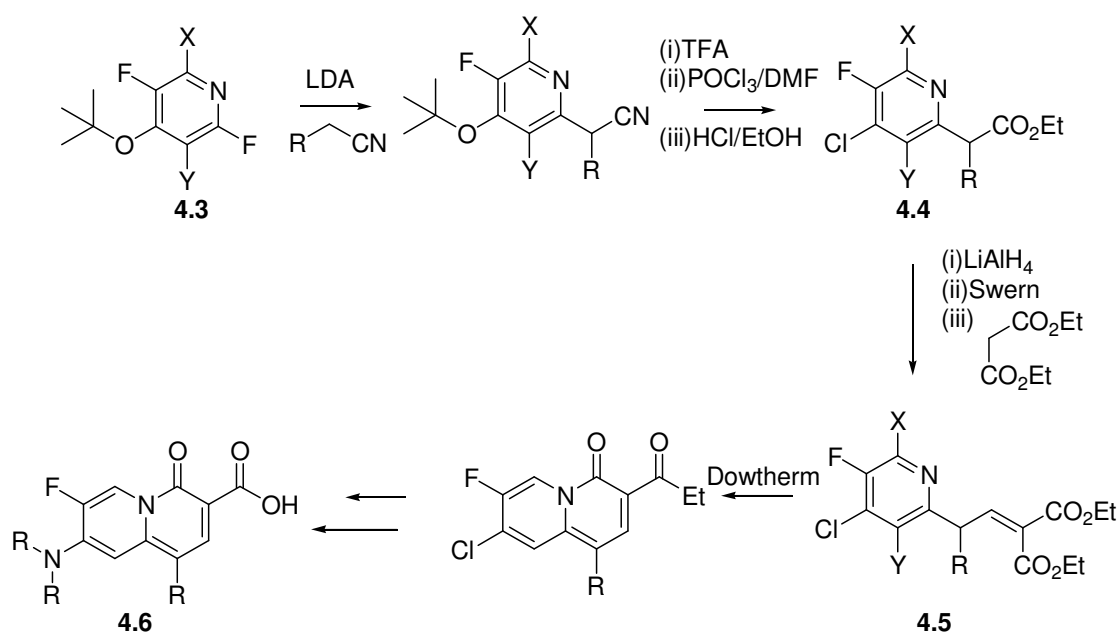


Figure 4.2 Ciprofloxacin and analogous quinolizinone structure

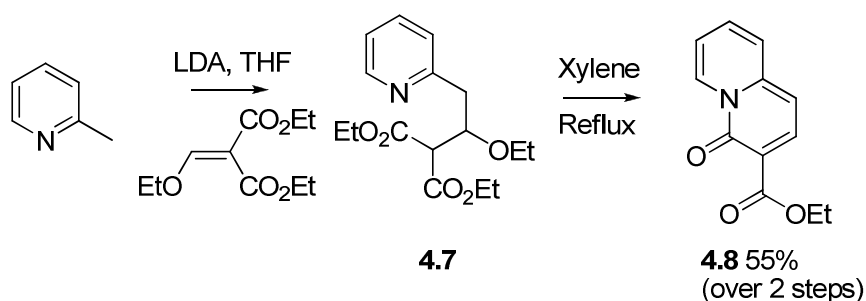
The synthesis began with the displacement of a fluoride of a substituted pyridine **4.3** with the appropriate nitrile. Removal of the *tert*-butyl group, displacement of the hydroxyl using phosphorus oxychloride and hydrolysis of the nitrile and esterification of the resulting acid gave the pyridyl acetate **4.4**. Reduction of the ester, oxidation using Swern conditions and condensation with diethyl malonate gave the cyclisation precursor **4.5**. The cyclisation was performed using conditions typical of quinolinone cyclisations, in refluxing Dowtherm. Two further steps were required to obtain the desired product **4.6** (Scheme 4.2)



Scheme 4.2 Synthesis of ciprofloxacin analogue **4.6**

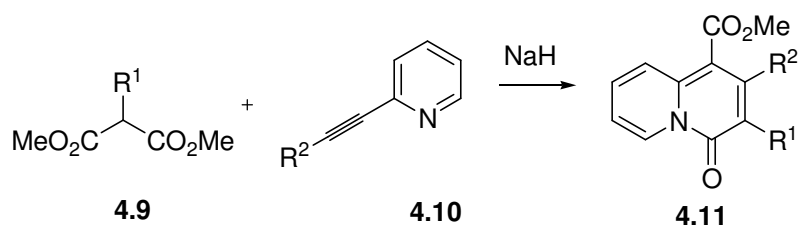
While clearly a target orientated synthesis, the number of steps required to obtain the cyclisation precursor **4.5** from pyridine **4.3** limits the scope of the methodology. This also does not include the number of steps required to synthesise pyridine **4.3**.

Other typical routes to quinolizinones involve the use of strong bases to deprotonate α -picolines. Investigating the potential of quinolizinones as magnesium ion selective fluorescent indicators, Levy et al⁶¹ synthesised a range of quinolizinones starting from substituted α -picolines, deprotonating the α -methyl using lithium diisopropylamide (LDA) and then adding diethyl ethoxymethylenemalonate to give the cyclisation precursor **4.7**. The cyclisation could be effected by refluxing the compound in xylene to give the quinolizinones **4.8** in moderate yields (Scheme 4.3)



Scheme 4.3 Levy's synthesis of quinolizinones from α -picolines

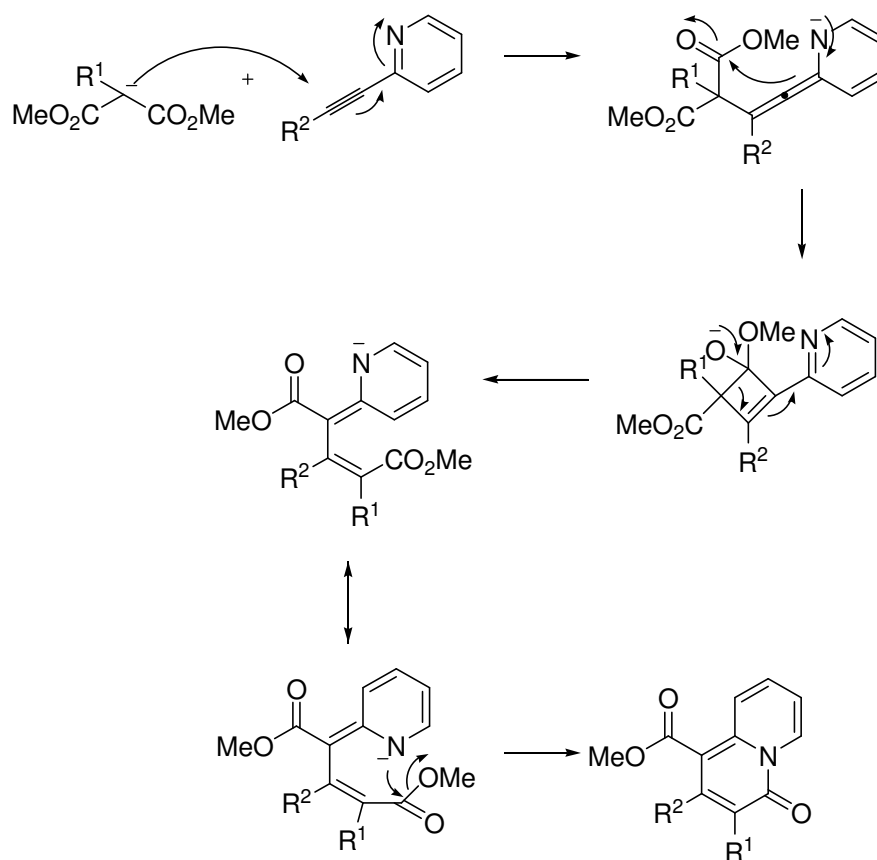
The reaction of malonate esters with alkynyl pyridines has been reported to generate 1,2,3-trisubstituted quinolizinones.⁶² Heating the appropriate malonate **4.9** and alkynylpyridine **4.10** with sodium hydride at 150 °C gave the quinolizinones **4.11** (Scheme 4.4)



Scheme 4.4 Synthesis of quinolizinones from alkynyl pyridines

The proposed mechanism for the formation of the quinolizinone involves the addition of the malonate anion to the alkyne. This then rearranges to give the cyclobutene, which ring opens to give the ester. This ester then cyclises to give the quinolizinone

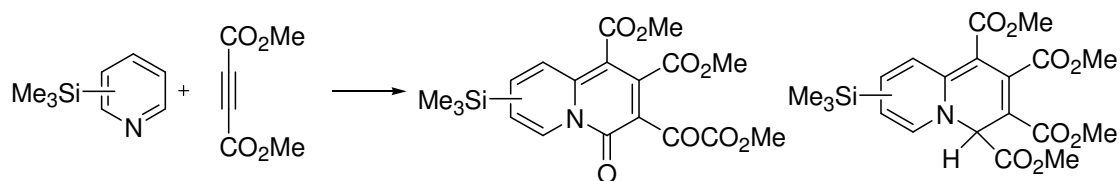
(Scheme 4.5)



Scheme 4.5 Mechanism of the formation of quinolizinones from alkynyl pyridines

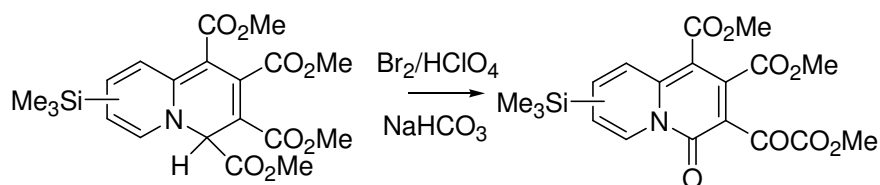
The yields for the process were typically 35 to 70% dependent on the alkyne and malonate used. However with some examples, a side product where the ester had been cleaved was observed and, for some examples, the starting materials (both the alkyne and malonate) would have to be synthesised, adding further steps to the reaction process.

Trimethylsilylpyridines react with dimethyl acetylenedicarboxylate to give quinolizinones and quinolizines (Scheme 4.6).⁶³



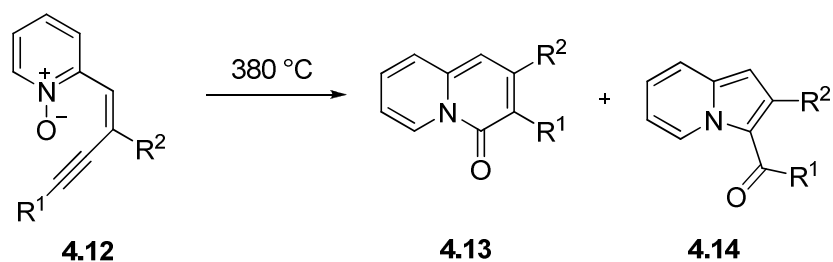
Scheme 4.6 Formation of quinolizinones from trimethylsilylpyridines and dimethyl acetylenedicarboxylate

The yields of quinolizinones from this reaction were generally very poor, around 5 – 15%, with around 30% of quinolizine formed. The quinolizines could be treated with bromine and perchloric acid to form the perchlorate salt, which when treated with sodium hydrogen carbonate gives the quinolizinone product (Scheme 4.7).



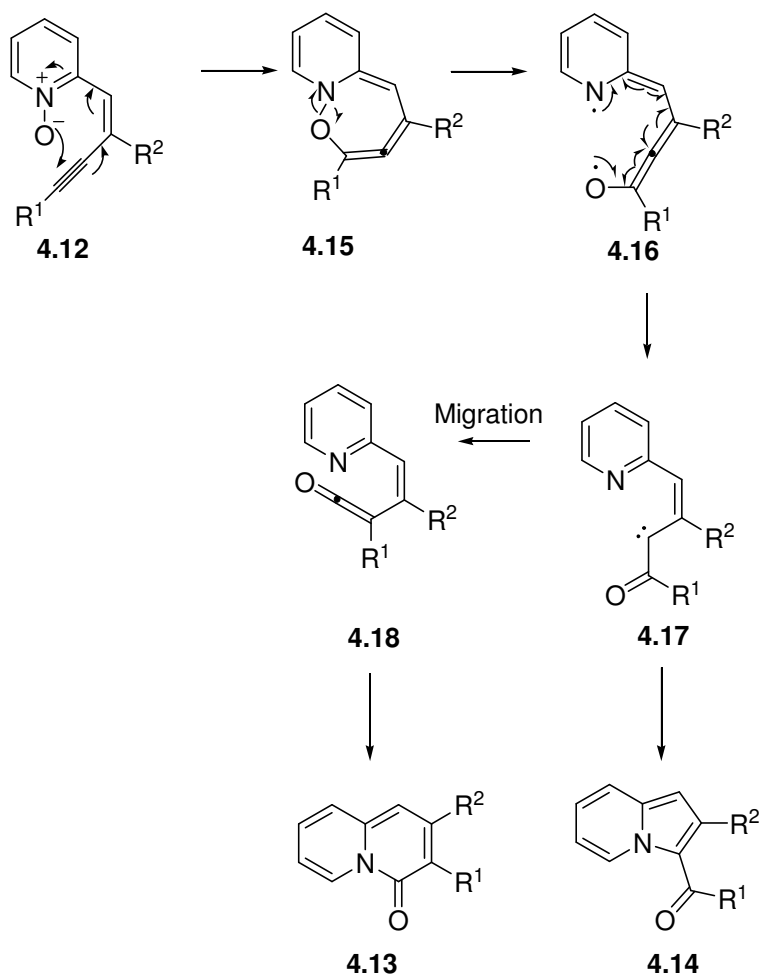
Scheme 4.7 Transformation of quinolizines to quinolizinones

Pyridine *N*-oxides have also been utilised in the formation of quinolizinones.⁶⁴ Heating butenyl pyridine *N*-oxides **4.12** under flow thermolysis conditions (380 °C, contact time of 10 seconds) gave two products: the substituted quinolizinone **4.13** and indolizine **4.14** (Scheme 4.8)



Scheme 4.8 Synthesis of quinolizinones and indolizinones from compound **4.12**

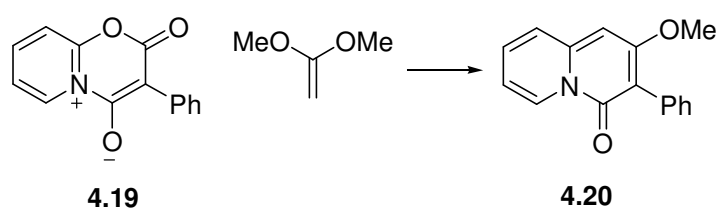
The proposed mechanism of the formation of the products initially involves an 8π electrocyclisation to generate the seven membered ring **4.15**. N-O bond cleavage leads to the formation of the carbene **4.17** from the diradical species **4.16**. The carbene can undergo a 6π electrocyclisation to give the indolizine **4.14**. Alternatively migration of the R^1 group gives the pyridyl ketene **4.18** which cyclises to give the quinolizinone product **4.13** (Scheme 4.9).



Scheme 4.9 Mechanism for the formation of compounds **4.13** and **4.14** from compound **4.12**

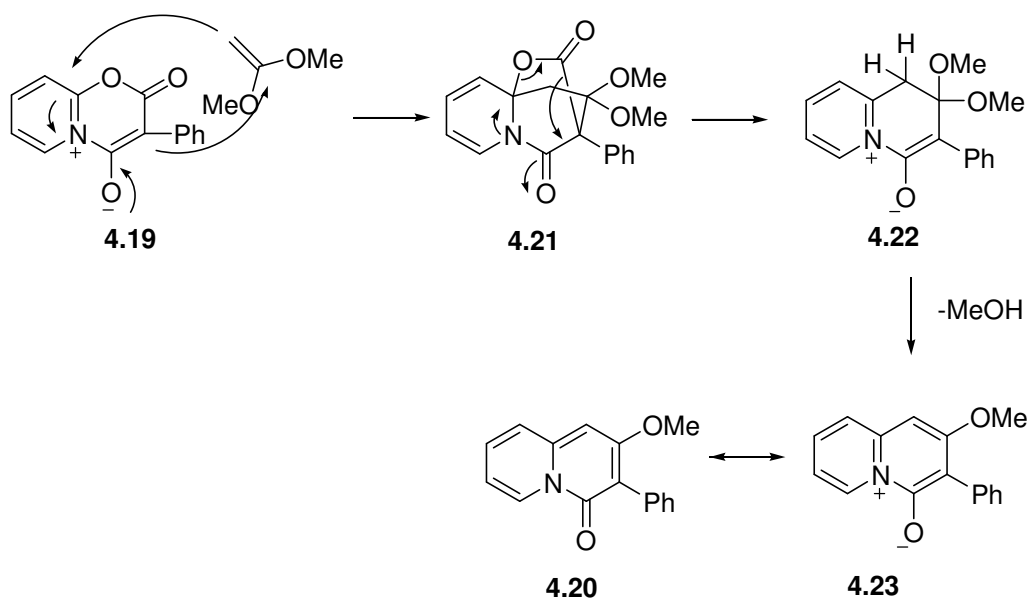
The ratio of quinolizinone **4.13** to indolizine **4.14** was between 2:1 and 6:1 depending on the substituents and overall yields of around 50-60% were obtained. The main drawback is the number of steps required to synthesise the starting N-oxide.

Dipolar cycloaddition reactions have also been used to synthesise quinolizinones.⁶⁵ Starting with betaine **4.19**, reaction with ketene dimethylacetal gave the quinolizinone **4.20** in 38% yield (Scheme 4.10)



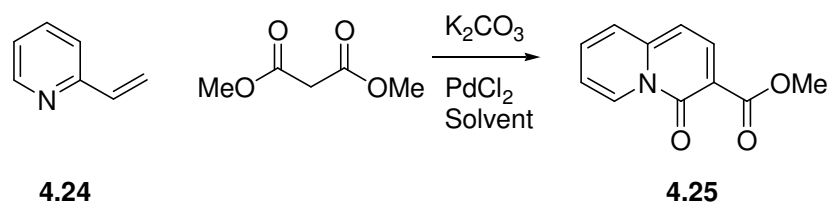
Scheme 4.10 Reaction of compound **4.19** to give compound **4.20**

The mechanism involves dipolar cycloaddition to give the adduct **4.21**, which undergoes decarboxylation to give the betaine intermediate **4.22**. This loses methanol to give structure **4.23**, which is a resonance structure of the quinolizinone (Scheme 4.11)



Scheme 4.11 Mechanism for the formation of compound **4.20**

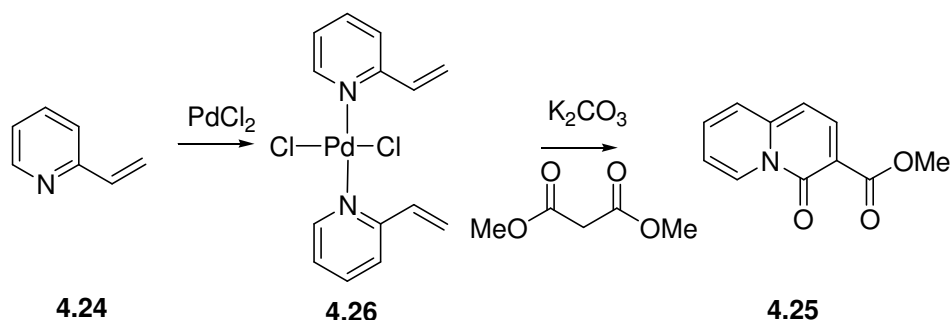
There is also a report of a palladium-catalysed synthesis of quinolizinones.⁶⁶ Heating 2-vinylpyridine **4.24**, dimethyl malonate, potassium carbonate and palladium (II) chloride in acetonitrile or DMF at 50 °C gave methyl quinolizinone-3-carboxylate **4.26** (Scheme 4.12).



Scheme 4.12 Palladium catalysed synthesis of compound **4.25**

No yields or catalyst loadings were mentioned for the one-pot synthesis. To study the role of the palladium in the reaction, the palladium (II) complex of 2-vinylpyridine **4.26** was obtained and exposed to same reaction conditions, resulting in the same

product (Scheme 4.13).



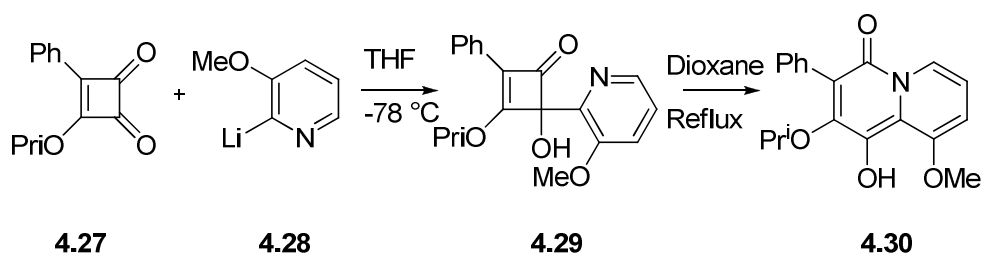
Scheme 4.13 Synthesis of palladium complex **4.26** and subsequent reaction to give compound **4.26**

Moderate yields of the quinolizinone were obtained from the reaction of the palladium complex with dimethyl malonate. However the drawback of the synthesis is the stoichiometric quantity of palladium required in the synthesis.

4.1.2 Synthesis of Hydroxyquinolizinones

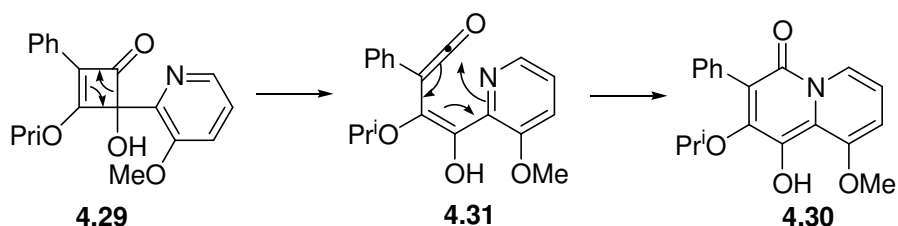
This section reviews the literature for the synthesis and properties of hydroxyquinolizinones. Hydroxyquinolizinones are an even rarer heterocycle than quinolizinones. Of the unsubstituted parent hydroxyquinolizinones, only two are known. Each of the seven possible regioisomers will be reviewed in order.

In the literature, the parent 1-hydroxyquinolizine is unknown. There is also only one reference to a substituted 1-hydroxyquinolizinone in the literature by Liebeskind.⁶⁷ This compound was synthesised from the substituted cyclobutadienone **4.27** and 2-lithio-3-methoxypyridine **4.28** to give the intermediate **4.29**. Heating this compound in dioxane results in the formation of the 1-hydroxyquinolizinone **4.30** in 48% yield over 2 steps (Scheme 4.14)



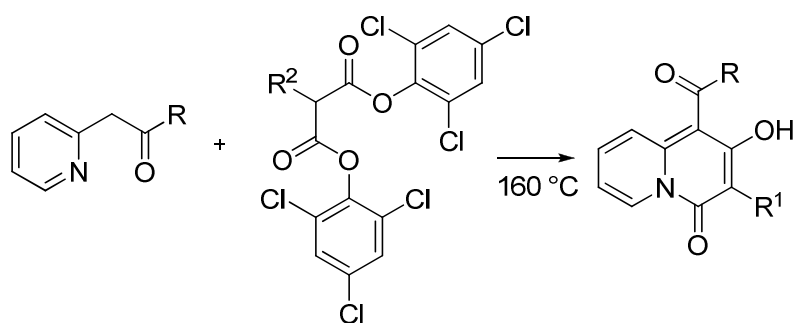
Scheme 4.14 Synthesis of 1-hydroxyquinolizinone **4.30**

The mechanism of formation of the quinolizinone involved a retro [2+2] cycloaddition reaction of the cyclobutenone **4.29** to give the pyridylketene **4.31**. This then undergoes an electrocycisation onto the pyridine nitrogen atom to give the quinolizinone **4.30** (Scheme 4.15). The other examples of this methodology involved *in situ* acetylation of the intermediate, leading to 1-acetoxyquinolizinones.



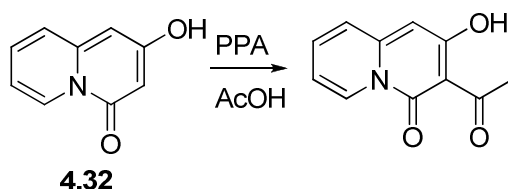
Scheme 4.15 Mechanism for the formation of compound **4.30**

A number of 2-hydroxyquinolizinones have been reported in the literature. Kappe and coworkers⁶⁸ reported the synthesis of 1-acyl-2-hydroxyquinolizinones, starting from a 2-picolylketone and trichlorophenyl malonate. A range of substituted 2-hydroxyquinolizinones was synthesised by varying the groups on the ketone and the malonate (Scheme 4.16)



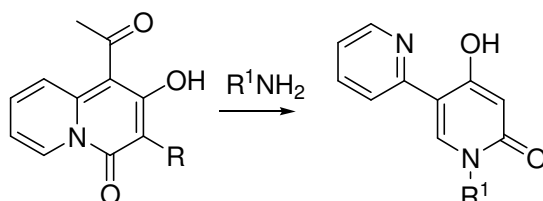
Scheme 4.16 Kappe's synthesis of 2-hydroxyquinolizinones

The 1-acyl group was found to be cleavable by boiling the hydroxyquinolizinones in hydrochloric acid. The reactions of the compounds were also explored, with acetylation of the hydroxyl group found to be possible with acetic anhydride and a catalytic amount of sodium acetate. Acylation of the parent compound **4.32** was also reported using polyphosphoric acid and acetic acid (Scheme **4.17**).



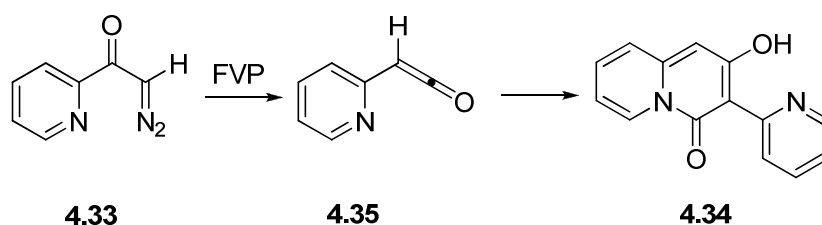
Scheme 4.17 Acylation of compound **4.32**

Rearrangement of the acylhydroxyquinolizinones using a substituted amine gave 1-substituted 4-hydroxy-5-pyridyl-2-pyridones, with small traces of the deacylated quinolizinones (Scheme **4.18**).⁶⁹



Scheme 4.18 Rearrangement of 2-hydroxyquinolizinones

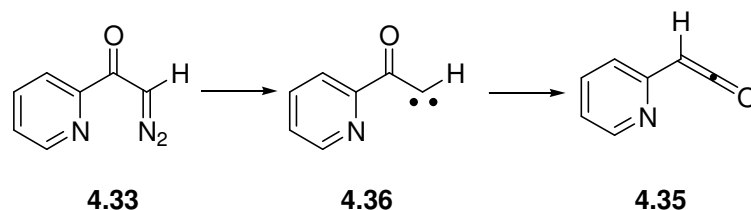
Dimerisation of pyridylketenes, generated by FVP of (2-diazoacetyl)pyridine **4.33** has been shown to result in 3-pyridyl-2-hydroxyquinolizinone **4.34** (Scheme **4.19**).⁷⁰



Scheme 4.19 Generation and dimerisation of pyridylketene **4.35**

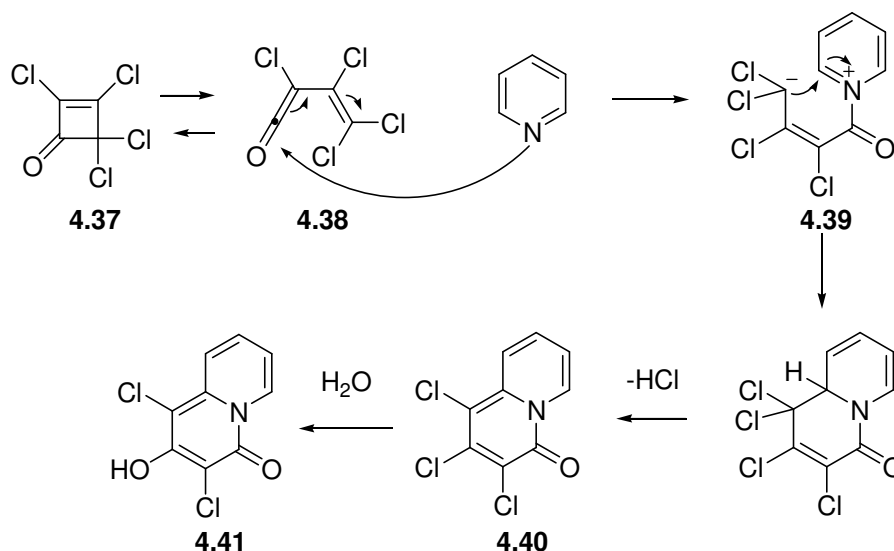
Matrix isolation studies on this pyrolysis show that, in the IR spectrum, the only product formed is pyridylketene **4.35**. The reaction was reported to be formally a

[2+4] cycloaddition of the two ketenes. Upon pyrolysis, the diazo compound **4.33** decomposes to give the carbene **4.36**, which undergoes a Wolff rearrangement to give the ketene **4.35** (Scheme 4.20).



Scheme 4.20 Generation of pyridylketene **4.35** from carbene **4.36**

The reaction of pyridines with tetrachlorocyclobutenone has been shown to give 2-hydroxyquinolizinones.⁷¹ The mechanism proceeds by ring opening of the cyclobutenone **4.37** to give the ketene **4.38**, which reacts with the pyridine to generate the dipolar intermediate **4.39**. Cyclisation of this intermediate and loss of HCl generates the trichloro-product **4.40**, which can be selectively hydrolysed to give the 2-hydroxyquinolizinone **4.41** (Scheme 4.21).

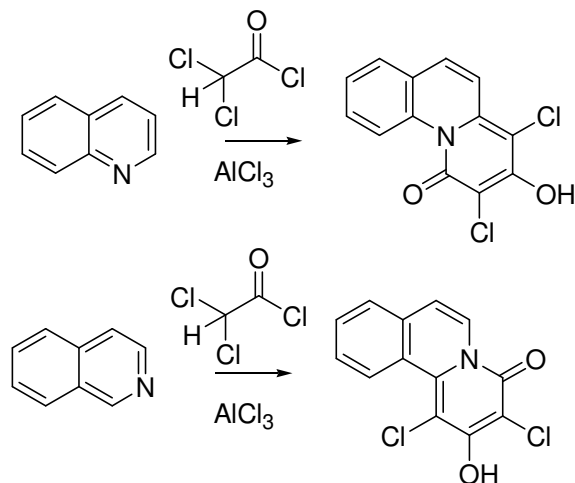


Scheme 4.21 Mechanism for the formation of compound **4.41**

The trichloroquinolizinones could also be isolated and displacement of the chlorine in the 2-position with an alcohol gave alkoxyquinolizinones in moderate yields.

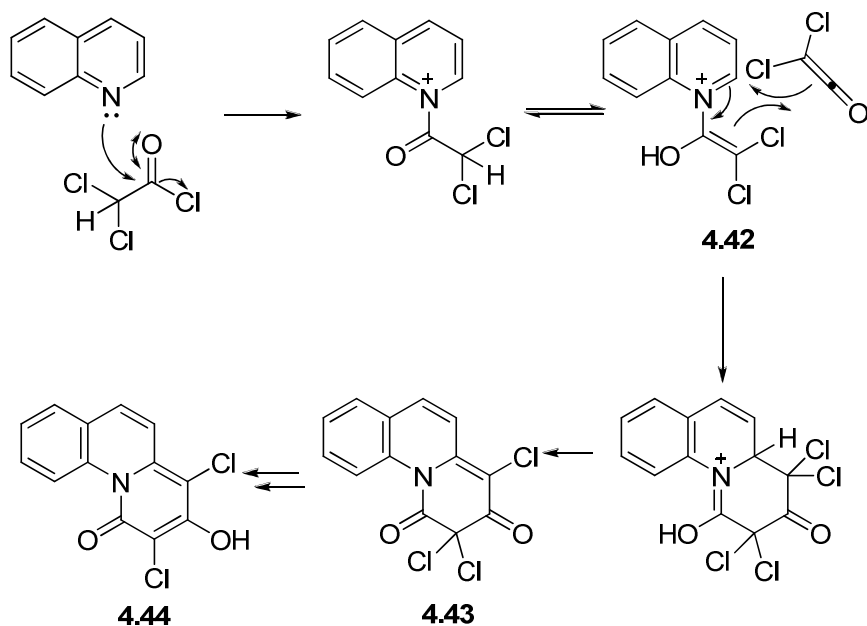
Benzo-analogues of substituted 2-hydroxyquinolizinones have also been reported.

The reaction of quinolines and isoquinolines with dichloroacetyl chloride in the presence of aluminium trichloride gave both benzo regioisomers of 1,3-dichloro-2-hydroxyquinolizinone in 75% and 66% yields respectively (Scheme 4.22).⁷²



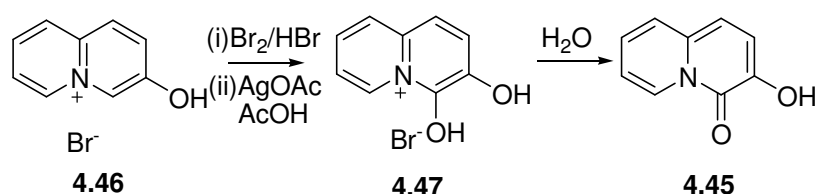
Scheme 4.22 Synthesis of two isomeric hydroxybenzoquinolizinones

The proposed mechanism for the formation of the benzoquinolizinones is shown in Scheme 4.23. The reaction of the nitrogen atom with dichloroacetyl chloride gives the acetylated product **4.42**. It is known that dichloroacetyl chloride can form dichloroketene *in-situ*. Here dichloroketene undergoes a [4+2] cycloaddition with the acetylquinoline to give intermediate **4.43**, which gives the benzohydroxyquinolizinone **4.44** on work-up.



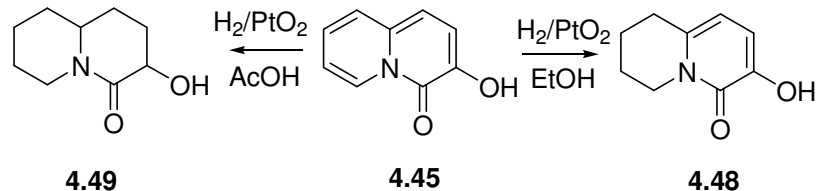
Scheme 4.23 Mechanism for the formation of compound **4.44**

The parent 3-hydroxyquinolizinone **4.45** is the only reported 3-hydroxyquinolizinone in the literature.⁷³ The product was synthesised from the dihydroxyquinolizinium bromide salt **4.47**, itself synthesised from 3-hydroxyquinolizinium bromide **4.46** by bromination in the 4-position and displacement of the bromine (Scheme 4.24)



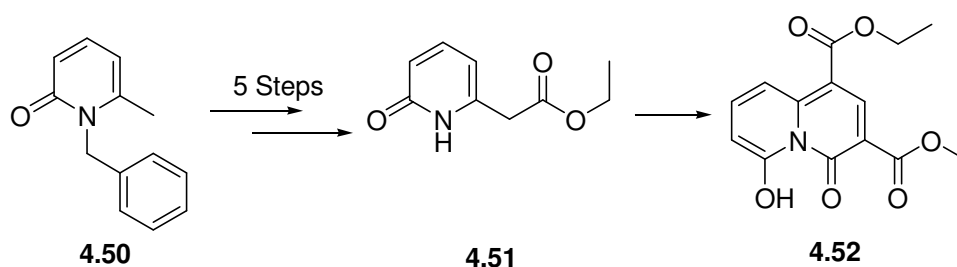
Scheme 4.24 Synthesis of 3-hydroxyquinolizinone **4.45**

Hydrogenation of 3-hydroxyquinolizinone **4.45**, using PtO_2 as a catalyst, was found to be dependent on solvent. In ethanol 3-hydroxy-6,7,8,9-tetrahydroquinolizinone **4.48** was obtained, where as in acetic acid the fully unsaturated quinolizidinone **4.49** was obtained (Scheme 4.25)



Scheme 4.25 Hydrogenation of 3-hydroxyquinolizinone **4.45**

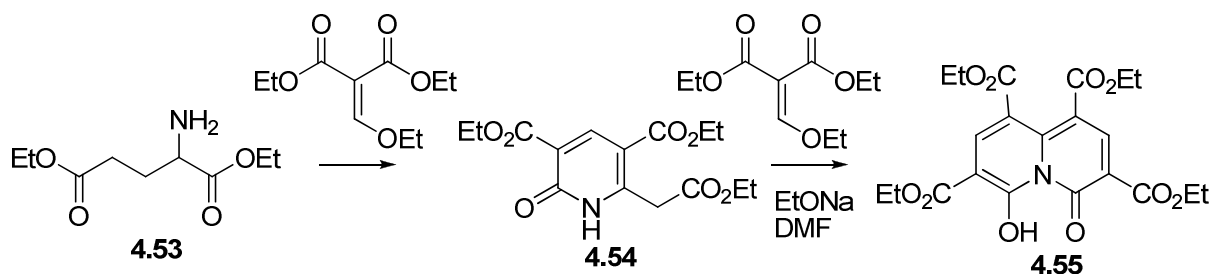
Reports of the 6-hydroxyquinolizinone are rare, with no reports of the synthesis of the parent ring system. Adams reported the synthesis of a substituted 6-hydroxyquinolizinone, starting from 1-benzyl-6-methyl-2-pyridone **4.50**.⁷⁴ Five steps were required to convert this compound into the cyclisation precursor **4.51**, and reaction with diethyl ethoxymethylenemalonate gives the 6-hydroxyquinolizinone **4.52** (Scheme 4.26).



Scheme 4.26 Synthesis of 6-hydroxyquinolizinone **4.52**

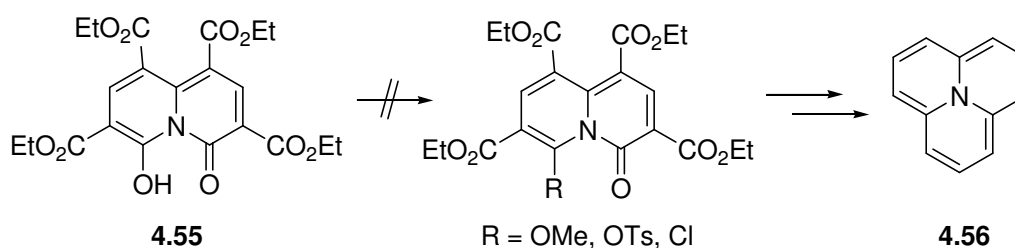
Attempts to reduce compound **4.52** with lithium aluminium hydride failed, only giving lithium salts of the quinolizinone. These lithium salts were found to be extremely stable, with sulfuric acid having no effect on the salt.⁷⁴

6-Hydroxyquinolizinones have also been targets in the synthesis of cycl[3,3,3]azine.⁷⁵ The starting point for the reaction was the substituted 2-pyridone **4.54**, which was synthesised in one step from diethyl β -aminoglutaconate **4.53** and diethyl ethoxymethylenemalonate. Heating the 2-pyridone, diethyl ethoxymethylene malonate and sodium ethoxide in DMF gave the hydroxyquinolizinone **4.55** as its sodium salt (Scheme **4.27**)



Scheme 4.27 Synthesis of compound **4.55**

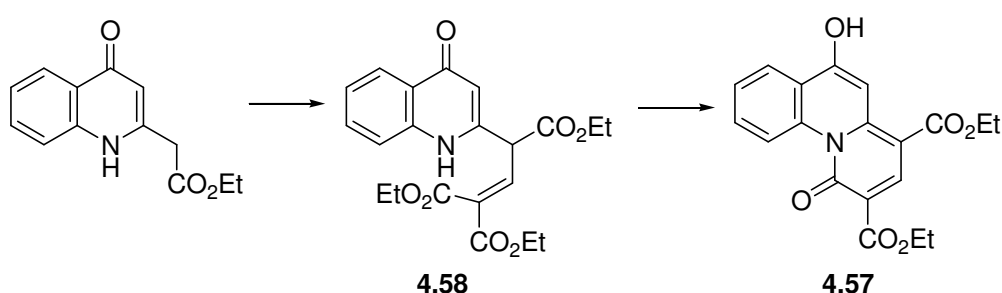
However, the original aim of converting the hydroxyquinolizinone **4.55** into cycl[3,3,3]azine **4.56** failed, due to the resistance of the hydroxyl group to methylation, sulfonylation or displacement with chloride (Scheme **4.28**)



Scheme 4.28 Attempted synthesis of cycl[3,3,3]azine **4.56**

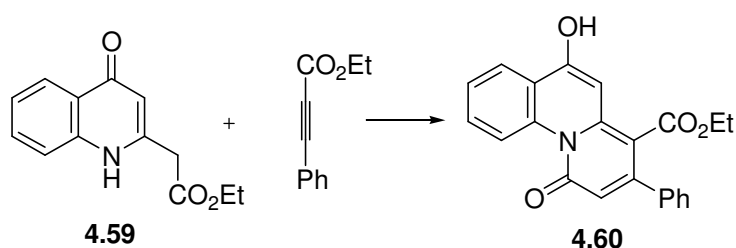
The unsubstituted 7-hydroxyquinolizinone has not been previously synthesised, and the few substituted examples reported are from patents with no information on how the hydroxyquinolizinones were synthesised or their characterisation data, merely on their reactions.⁷⁶

The parent 8-hydroxyquinolizin-4-one is unknown, but some analogues have been reported. A substituted benzo- analogue **4.57** has been reported,⁷⁷ synthesised from a 2-substituted quinolin-4-one **4.58**, followed by cyclisation onto the nitrogen in the 1-position to give the benzoquinolizinone **4.57** (Scheme 4.29)



Scheme 4.29 Synthesis of hydroxybenzoquinolizinone **4.57**

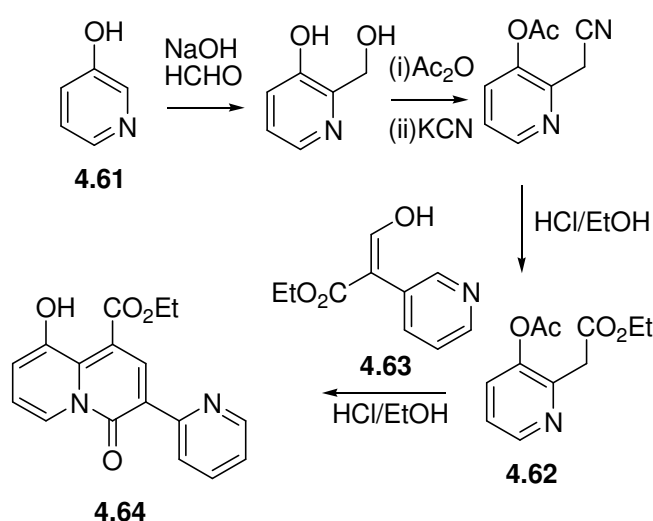
With both the 1- and 3-positions blocked in molecule **4.57**, bromination was observed to occur in the position *ortho* to the hydroxyl group (the 9-position in the parent system) from the ¹H NMR spectrum of the crude material, but isolation of the bromo compound proved impossible. Similarly, reaction of compound **4.59** with ethyl phenylpropiolate gave the 1,2 disubstituted product **4.60**, by conjugate addition to the alkyne followed by cyclisation to give compound **4.60** (Scheme 4.30)



Scheme 4.30 Synthesis of compound **4.60**

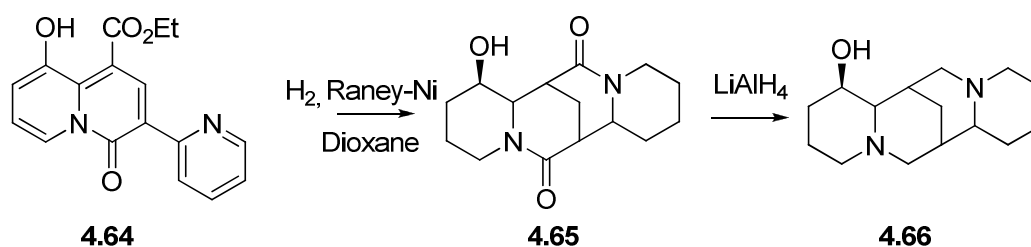
The parent 9-hydroxyquinolizinone is unknown in the literature, and again most of the substituted examples reported in the literature are in patents with no synthetic detail or

characterisation data, only reactions of the compound.⁷⁶ A substituted 9-hydroxyquinolizinone was synthesised as an intermediate in the synthesis of a hydroxyspartiene alkaloid.⁷⁸ The synthesis starts with the reaction of 3-hydroxypyridine **4.61** with formaldehyde to introduce a hydroxymethyl group in the 2-position. Acetylation of the phenol and hydroxyl groups, followed by displacement with potassium cyanide gives the nitrile, which can be hydrolysed and esterified to give the activated α -picoline **4.62**. Condensation with compound **4.63** gave the 9-acetoxyquinolizinone, which was hydrolysed to give the 9-hydroxyquinolizinone **4.64** (Scheme 4.31)



Scheme 4.31 Synthesis of substituted 9-hydroxyquinolizinone **4.64**

The 9-hydroxyquinolizinone **4.64** was hydrogenated using Raney-nickel at 180 °C and 250 atmospheres of hydrogen to give the cyclised bilactam **4.65**, which was reduced with lithium aluminium hydride to give the natural product **4.66** (Scheme 4.32).



Scheme 4.32 Synthesis of hydroxyspartiene alkaloid **4.66** (other stereocentres are unspecified).

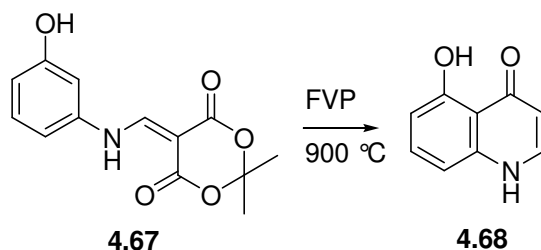
4.1.3 Conclusion

A number of synthetic routes to quinolizinones and hydroxyquinolizinones have been published. These have required multistep reactions to synthesise the starting materials, which leads to low overall yields due to the number of steps required. A number of these reactions are also only applicable to the synthesis of quinolizinones with additional groups, typically electron-withdrawing groups such as esters, which may require additional steps to remove.

4.2 Results and Discussion

4.2.1 Synthesis of 8-Hydroxyquinolizinones

As discussed in the previous chapter, the pyrolysis of compound **4.67** at 900 °C leads to the formation of 5-hydroxyquinolinone **4.68** exclusively (Scheme 4.33).



Scheme 4.33 Pyrolysis of compound **4.67** at 900 C

The temperature required to effect the conversion to 5-hydroxyquinolinone **4.68** was also found to be much higher than usual, 900 °C rather than the typical 600 °C used for these reactions. At lower temperatures, a different product was observed which at 500 °C was the sole isolated product from the pyrolysis. This product showed six aromatic ^1H NMR signals, with the presence of both a triplet and a singlet excluding both 5- and 7-hydroxyquinolinones as possible structures. In addition, a doublet was observed at $\delta_{\text{H}} = 8.96$ ppm, much higher in chemical shift than would be expected for a hydroxyquinolinone. The ^{13}C DEPT spectrum showed the presence of 6 CH resonances, with the ^{13}C NMR spectrum showing the presence of 3 quaternary carbons. The carbonyl group, typically at $\delta_{\text{C}} = 170 - 175$ ppm in the ^{13}C NMR spectrum of quinolinones, is at $\delta_{\text{C}} = 159$ ppm in this product. This suggests that the compound does not possess a quinolinone structure and could be an amide rather than a quinolinone carbonyl. The mass spectrum of the compound gave a molecular ion with $m/z = 161$, which indicates that the compound is isomeric with 5-hydroxyquinolinone **4.68**.

A COSY experiment was also performed and showed the following signals (Table 4.1)

Proton	δ_H /ppm	Correlations
A	8.96	C/D, E (weak)
B	7.53	E, F
C/D	6.95 – 6.85	A
E	6.52	B, F, A (weak)
F	6.04	B, E

Table 4.1 COSY correlation data for the unidentified product

The COSY experiment shows that protons A and either C or D are in the same spin system, as are protons B, E and F. A weak correlation between protons A and E suggest that the protons are in a “W” configuration across the ring junction. This gives the partial structure in figure 4.3.

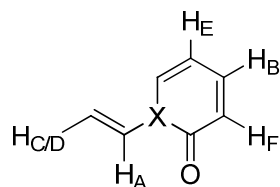


Figure 4.3 Substructure deduced from COSY data

A NOESY experiment was performed to assign the ^1H NMR spectrum fully (Figure 4.4).

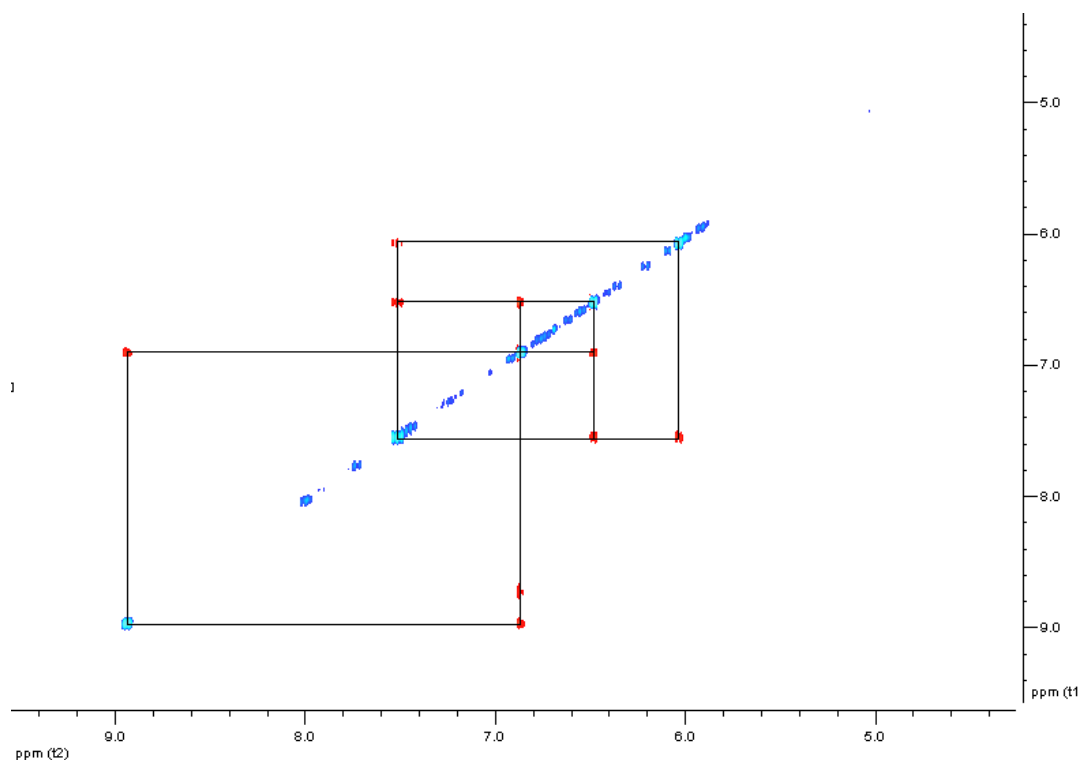


Figure 4.4: NOESY (360 MHz) of compound 4.69

Proton	δ_H /ppm	Correlations
A	8.96	C/D
B	7.53	E, F
C	6.95 – 6.85	A, E
D		
E	6.52	C/D, B
F	6.04	B

Table 4.2 NOESY correlation data of compound **4.69**

The NOESY shows that the proton at $\delta_H = 6.52$ ppm shows an interaction to one of the protons in the multiplet at $\delta_H = 6.95 - 6.85$ ppm. This correlation gives the substructure shown in figure **4.5**.

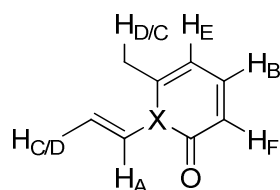


Figure 4.5 Substructure of compound **4.69** deduced from NOESY data

From the mass spectrum and ^{13}C data, there is one quaternary carbon, one nitrogen, one oxygen and one hydrogen atom left to assign. X must therefore be the nitrogen, with the remaining carbon being substituted with a hydroxyl group. This gives 8-hydroxyquinolizinone **4.69** as the product (Figure **4.6**)

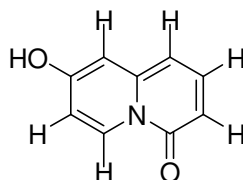


Figure 4.6 Structure of 8-hydroxyquinolizinone **4.69**

This structure is consistent with the NMR data of the product and the ring system was confirmed by an X-ray crystal structure of an analogue (see later) and by removal of the hydroxy group to give quinolizinone, a known compound (see later).

The temperature profile of the Meldrum's acid derivative **4.67** for the reaction is shown below (Figure 4.7).

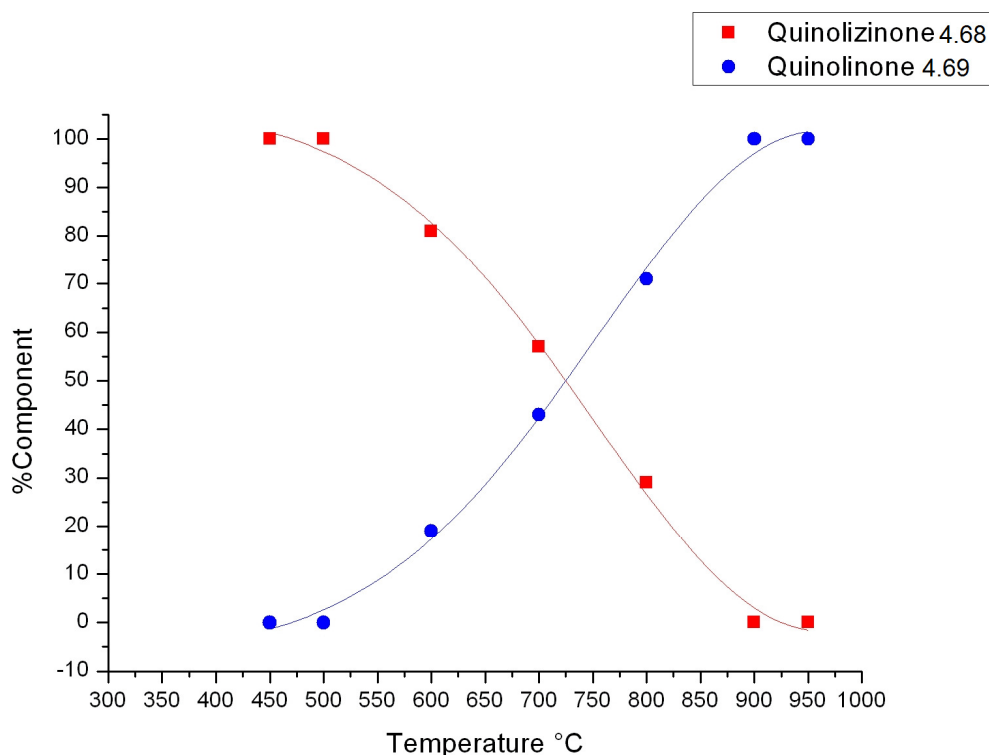
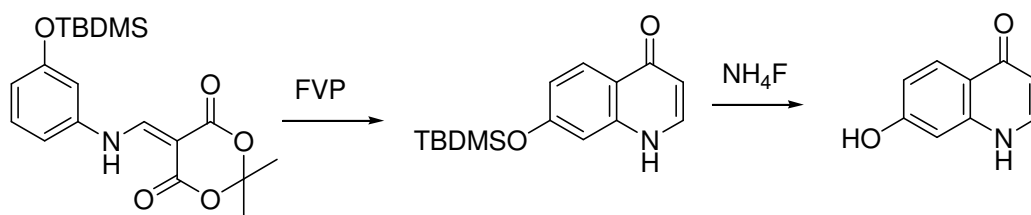


Figure 4.7 Temperature profile data for compounds **4.68** and **4.69**

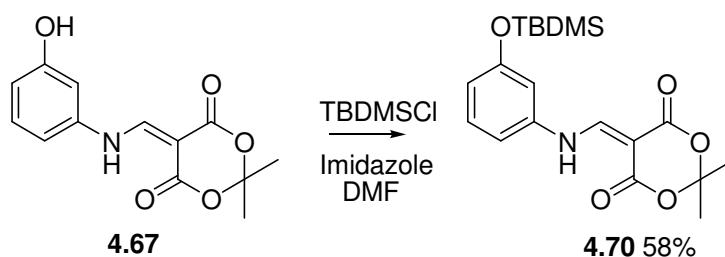
From Figure 4.7, it can be seen that there is control over the reaction, below 500 °C the isolated product is 8-hydroxyquinolizininone **4.68** and at temperatures above 900 °C, 5-hydroxyquinolinone **4.69** was isolated. This result makes this a good synthetic route to compounds **4.68** and **4.69**.

In order to show conclusively that the compound was not 7-hydroxyquinolinone, 7-hydroxyquinolinone was synthesised by a different method. The initial strategy involved the protection of the hydroxyl group by an easily removable group. The *tert*-butyldimethylsilyl group was chosen, due to the ease of removal using tetrabutylammonium fluoride. The steric bulk of the protecting group should steer the cyclisation towards the 7-position and subsequent deprotection should give 7-hydroxyquinolinone (Scheme 4.34)



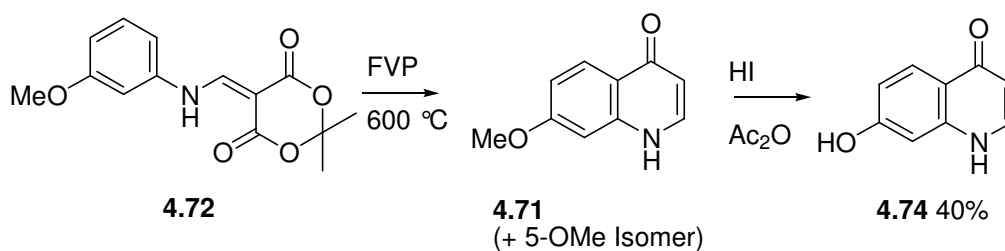
Scheme 4.34 Proposed synthesis of 7-hydroxyquinolinone

The precursor **4.70** was synthesised from the hydroxy-compound **4.67** using DMF, imidazole and TBDMS chloride in 58% yield (Scheme 4.35).



Scheme 4.35 Preparation of the compound **4.70**

However pyrolysis of compound **4.70** at 600 °C lead to the formation of yellow oil, with no identifiable products in the ^1H NMR spectrum, hinting at the possible instability of the silyl protecting group under FVP conditions. An alternative strategy was employed, using demethylation of 7-methoxyquinolinone **4.71**. Pyrolysis of methoxy-compound **4.72** led to the formation of the 7-methoxy- and 5-methoxyquinolinones **4.71** and **4.73** in a 9:1 ratio (Chapter 3). Recrystallisation of the crude pyrolysate from methanol gave a clean sample of 7-methoxyquinolinone **4.71** (See compound **3.55**, chapter 3, page 145) for the subsequent demethylation reaction. Demethylation was achieved by reaction with acetic anhydride and hydroiodic acid⁷⁹ and 7-hydroxyquinolinone **4.74** was obtained in 40% yield (Scheme 4.36)

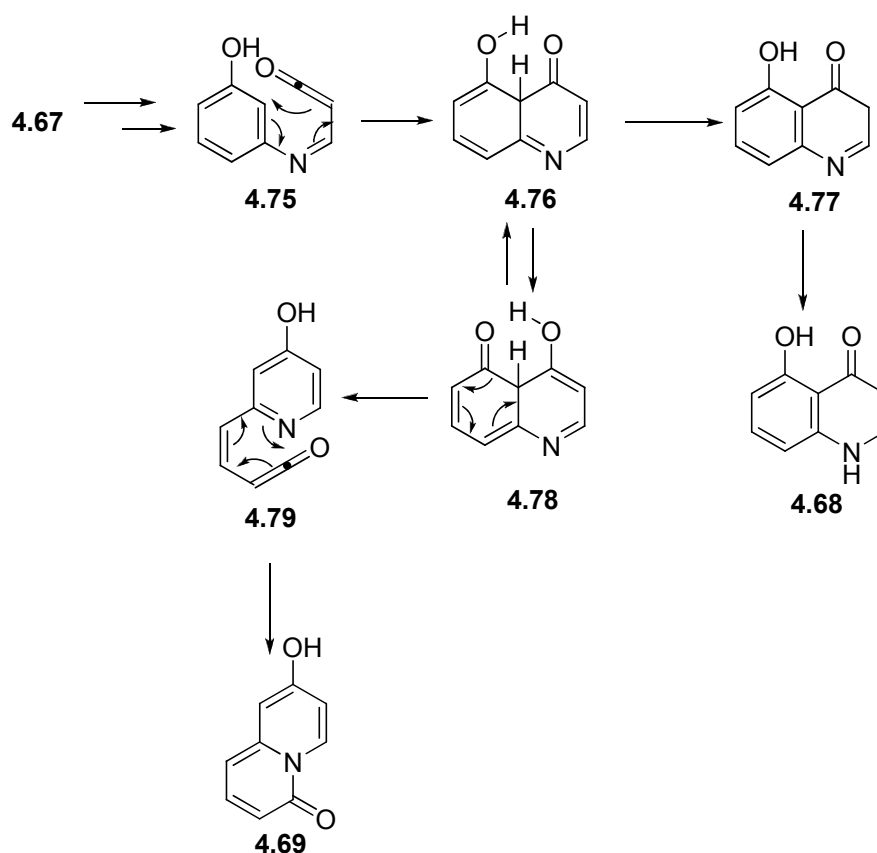


Scheme 4.36 Synthesis of 7-hydroxyquinolinone **4.74**

The ^1H NMR spectrum of 7-hydroxyquinolinone **4.74** did not show the presence of the doublet at $\delta_{\text{H}} = 9.0$ ppm and the ^{13}C NMR spectrum showed the carbonyl to have a resonance at $\delta_{\text{H}} = 172$ ppm.

4.2.2 Mechanism

A suggested mechanism for the formation of 8-hydroxyquinolizinone **4.69** from compound **4.67** is shown in scheme 4.37.

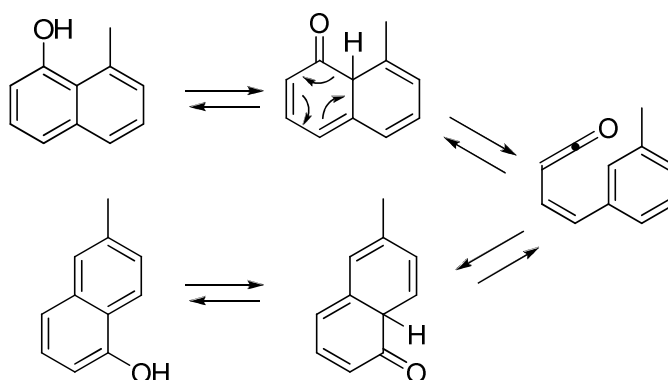


Scheme 4.37 Mechanism of the formation of 8-hydroxyquinolizinone **4.69**

The initial cyclisation reaction of the imidoylketene **4.75** is the same as for 5-hydroxyquinolinone to give intermediate **4.76**. Intermediate **4.76** can go through two possible reaction mechanisms. A 1,5 hydrogen shift generates intermediate **4.77**, which can undergo a 1,3 hydrogen shift to give 5-hydroxyquinolinone **4.68**. Alternatively, tautomerism of the hydroxy- hydrogen atom can give the 4-hydroxypyridine-like intermediate **4.78**, which can then undergo a retro-

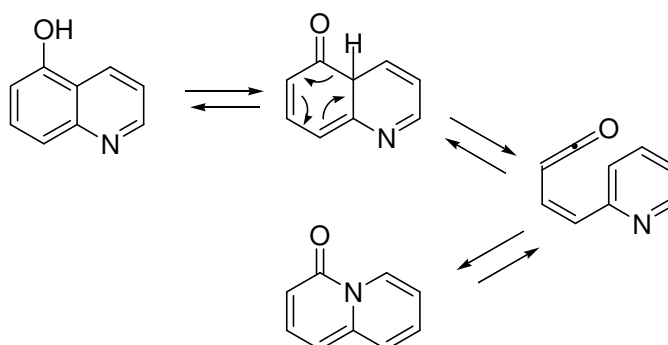
electrocyclisation to generate pyridyl ketene **4.79**. Cyclisation of **4.79** onto the pyridine nitrogen then gives 8-hydroxyquinolizinone **4.69**.

Work by Dreiding⁸⁰ has shown that the flow pyrolysis of 8-methylnaphth-1-ol gave significant quantities of 6-methylnaphth-1-ol. The proposed mechanism involved the formation of a ketene intermediate, which could then cyclise onto the position *meta* to its original location (scheme **4.38**)



Scheme 4.38 Mechanism for the pyrolysis of 8-methylnaphth-1-ol

It could therefore be envisaged that pyrolysis of 5-hydroxyquinoline may give quinolizinone *via* a similar mechanism (Scheme **4.39**).



Scheme 4.39 Proposed mechanism for the pyrolysis of 5-hydroxyquinoline

Pyrolysis of 5-hydroxyquinoline at both 500 °C and 900 °C showed no signs of quinolizinone formed by ¹H NMR spectroscopy, only the presence of starting material. This could be due to the hydroxyquinoline being the thermodynamic product of the reaction, thus the rearrangement to give quinolizinone would not occur under thermal (FVP) conditions.

This is further demonstrated by the repyrolysis of 8-hydroxyquinolizinone **4.69**, the temperature profile of which is shown below (Figure **4.8**).

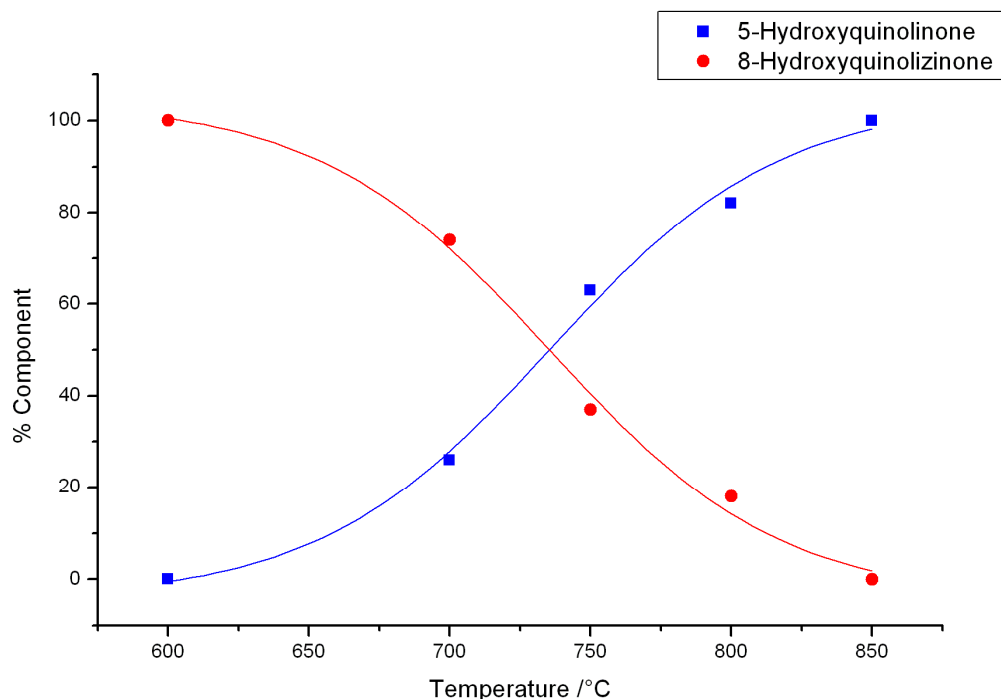
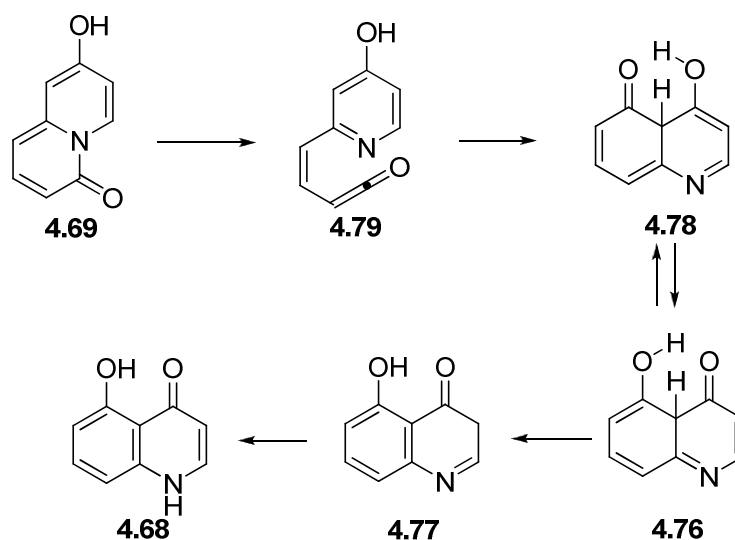


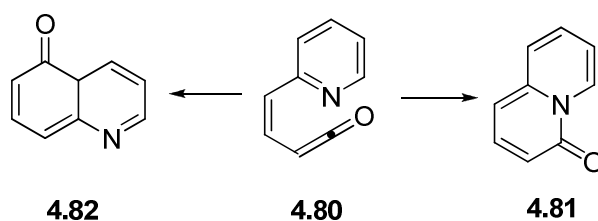
Figure 4.8 Repyrolysis temperature profile of 8-hydroxyquinolizinone **4.69**

At higher furnace temperatures, the only observed product is 5-hydroxyquinolinone **4.68**. The repyrolysis did show signs of decomposition, due to the high inlet temperatures required to volatilise the starting material. What this shows is that the kinetic product can reform the intermediate **4.76** and possess enough energy to undergo the 1,5-hydrogen shift, and form the thermodynamic product, 5-hydroxyquinolinone **4.68** (Scheme **4.40**)



Scheme 4.40

In order to confirm the feasibility of the proposed mechanism, DFT calculations were employed. Previous DFT calculations⁸¹ have shown that the cyclisation of pyridyl ketene **4.80** to quinolizinone **4.81** is pseudo-pericyclic, preceeding with no energy barrier, and that the cyclisation onto the carbon atom to give **4.82** has an energy barrier of 88 kJ mol⁻¹ (Scheme 4.41)



Scheme 4.41 Cyclisation modes of pyridylketene **4.80**

The calculations for the formation of 8-hydroxyquinolizinone were performed at B3LYP/6-31G** level using Gaussian03.⁸² The energy surface is shown in figure 4.9.

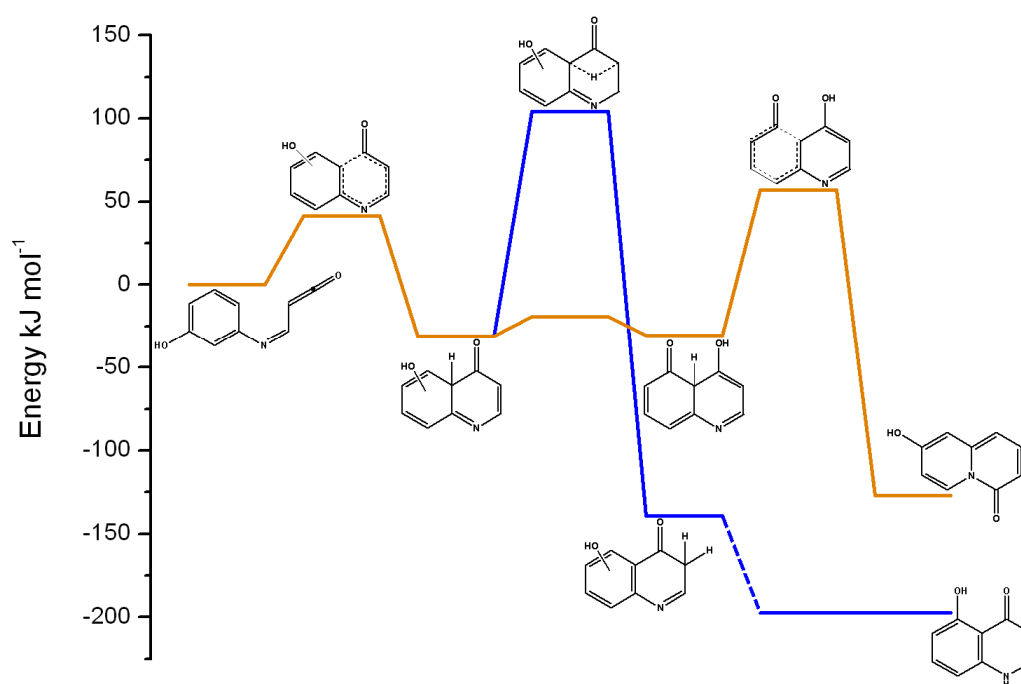


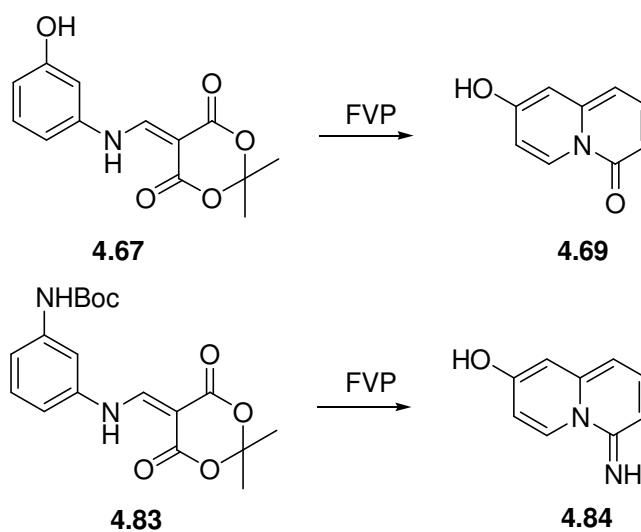
Figure 4.9 Energy surface for the formation of compounds **4.68** and **4.69**

The initial cyclisation has a barrier of 40 kJ mol^{-1} , leading to intermediate **4.76**. At this point the 1,5-hydrogen shift has a large energy barrier of 142 kJ mol^{-1} , which makes it the rate-determining step in the formation of 5-hydroxyquinolinone **4.68**, while the proton transfer has a small barrier of 11 kJ mol^{-1} . The barrier to form the pyridyl ketene **4.79** is 88 kJ mol^{-1} and, as found by Cabaleiro-Lago, the cyclisation to the quinolizinone **4.69** has no energy barrier and is pseudo-pericyclic.⁸¹

The calculations show that at low furnace temperatures, the reaction follows the lower energy pathway, due to the large energy involved in the 1,5 hydrogen shift, to give the kinetic product, 8-hydroxyquinolizinone **4.69**. At higher furnace temperatures, there is sufficient energy in the system to overcome the energy barrier to the hydrogen shift and the more thermodynamically stable product, 5-hydroxyquinolinone **4.68**, is formed.

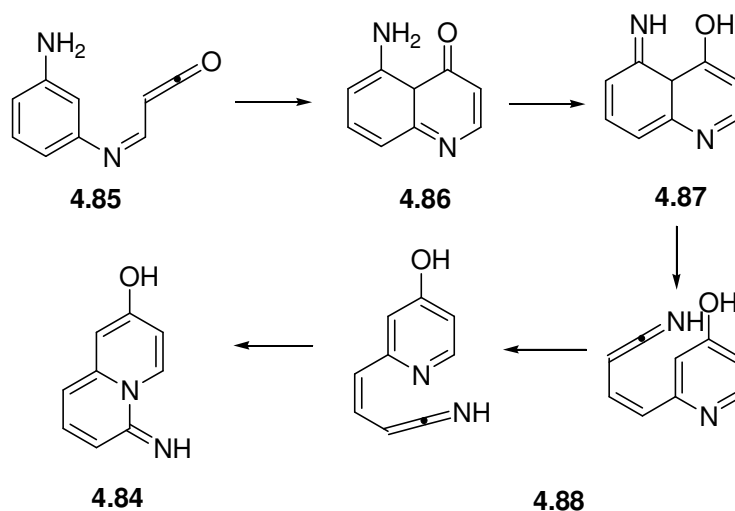
An interesting aspect of the mechanism is why only the hydroxy- substituted compound **4.67** shows this behaviour. It could be envisaged that the amino compound **4.83** might undergo a similar mechanism to give the quinolizinone imine

4.84 (Scheme 4.42).



Scheme 4.42 Proposed formation of quinolizine imine **4.84**

From chapter 3, this is known not to be the case. Quinolizine imines such as structure **4.84** are known in the literature.⁵⁹ The mechanism, however, would involve the formation of a ‘ketenimine’ **4.88**, which would cyclise to give the imine product **4.84** (Scheme 4.43)



Scheme 4.43 Mechanism for the formation of the quinolizine imine **4.84**

The energy surface for the hypothetical reaction was modelled using DFT calculations at B3LYP/6-31G** level and the surface is shown below (Figure 4.10)

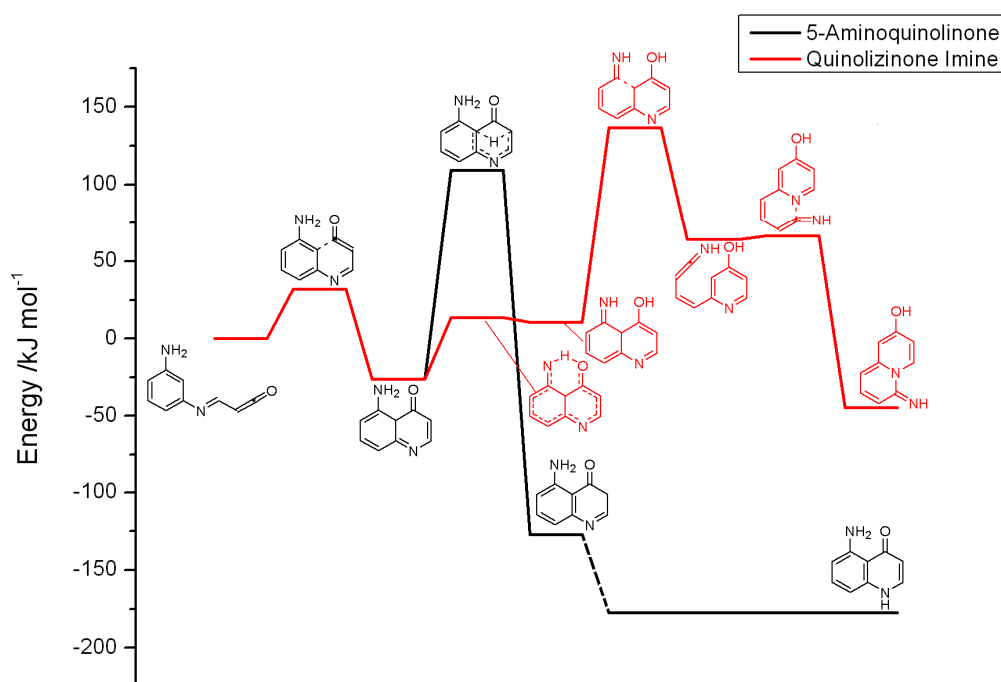


Figure 4.10 Energy surface for the formation of quinolizone imine **4.84**

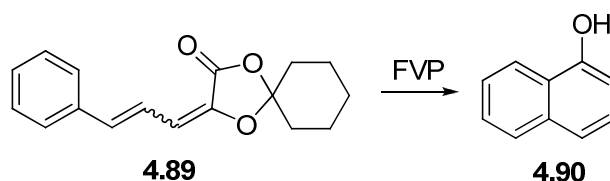
From figure **4.10**, the reason the quinolizone imine **4.84** does not form becomes apparent. The hydrogen transfer to give the imine intermediate **4.87** has a larger barrier (around 24 kJ mol^{-1}), but is still lower than the 1,5 hydrogen shift. The formation of the ketenimine **4.88**, however, has a barrier that is higher than the 1,5 hydrogen shift. This energy barrier prevents the formation of the ketenimine, meaning that the 1,5 hydrogen shift dominates the reaction and forms the quinolinone product. In the formation of the quinolizone imine **4.84**, the cyclisation reaction is now no longer pseudopericyclic and possesses a small energy barrier of around 2 kJ mol^{-1} .

4.2.3 Alternative Direct Route to Pyridylketenes

In order to demonstrate the mechanism and the possibility of the pyridylketene cyclising to give quinolizones, an alternative route to the pyridylketene was required.

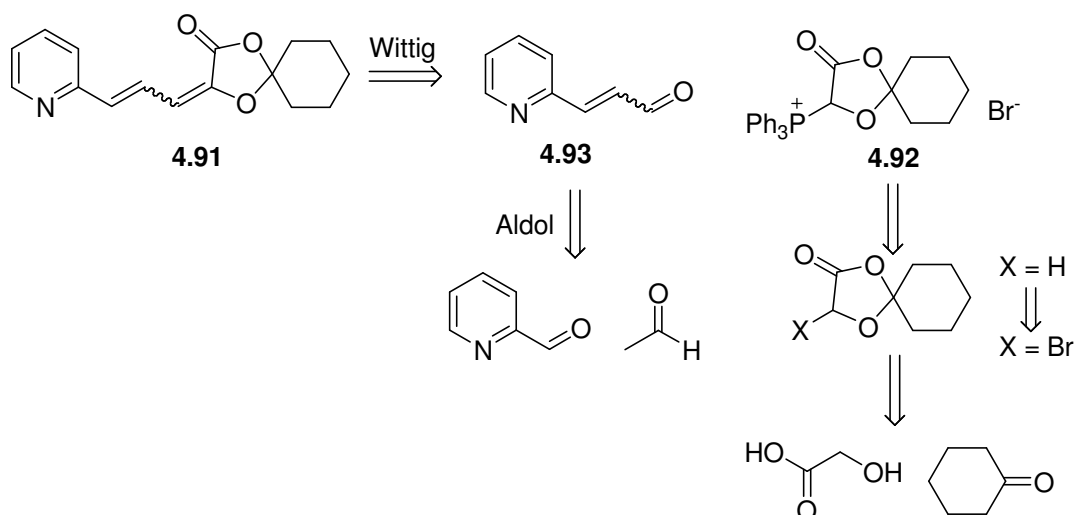
Unpublished work within the McNab⁸³ group has shown that precursors based on dioxolanes, such as **4.89**, can generate ketenes that participate in cyclisation reactions,

in this case cyclising to give 1-naphthol **4.90** (Scheme 4.44). 5,5-Disubstituted dioxolanones have also been used to generate ketones under FVP conditions.⁸⁴



Scheme 4.44 Pyrolysis of compound **4.89**

Using this reaction and replacing the phenyl ring with a pyridine, it should be possible to generate the pyridylketene directly. The retrosynthesis of the pyrolysis precursor **4.91** is shown below (Scheme 4.45)

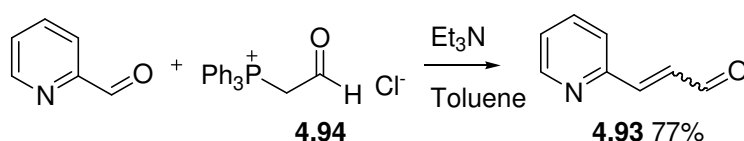


Scheme 4.45 Retrosynthesis of compound **4.91**

The synthesis of the dioxolane fragment **4.92**, starting from glycolic acid and cyclohexanone, and its Wittig reactions have been reported in the literature by Ramage.⁸⁵ The pyridyl fragment **4.93** has also been reported in the literature from the aldol reaction of pyridine-2-carboxaldehyde and acetaldehyde, though in low yield (14%).

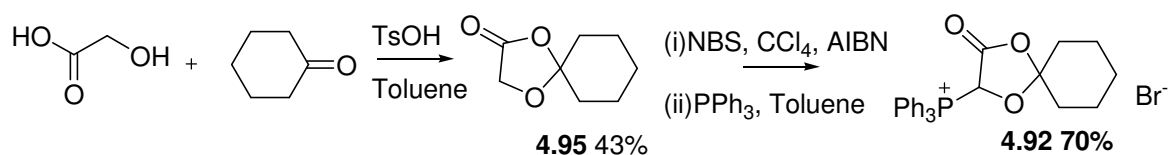
Following the literature aldol reaction of pyridine-2-carboxaldehyde and acetaldehyde resulted in a black oil, which contained a small amount of the desired product. Based on the mass of the recovered material, the yield after purification would have been

extremely low (less than 5%). An alternative route to the desired compound was required. Wittig reactions of (formylmethyl)triphenylphosphonium chloride **4.94** have been reported using triethylamine in benzene⁸⁶ and application of these conditions (with toluene in place of benzene) led to the formation of the desired product **4.93** in 77% yield, as a 9:1 mixture of double bond isomers (Scheme 4.46), which were not identified due to similarities in the coupling constants in the alkene protons.



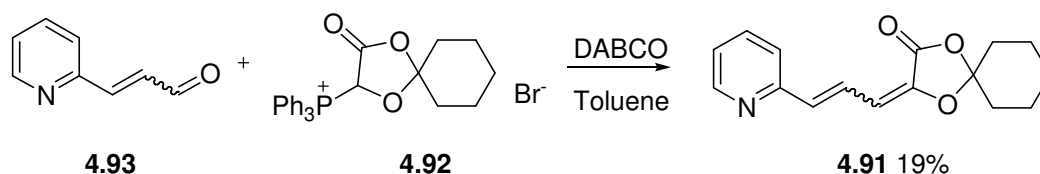
Scheme 4.46 Synthesis of compound **4.93** by Wittig reaction

The dioxolane fragment **4.92** was synthesised by the literature method.⁸⁵ Condensation of cyclohexanone and glycolic acid, using a catalytic amount of *p*-toluenesulfonic acid gave the dioxolane **4.95** in 43% yield after purification. Radical bromination, using *N*-bromosuccinimide, AIBN and CCl₄, followed by addition of triphenylphosphine gave the phosphonium salt **4.92** in a crude 70% yield (Scheme 4.47).



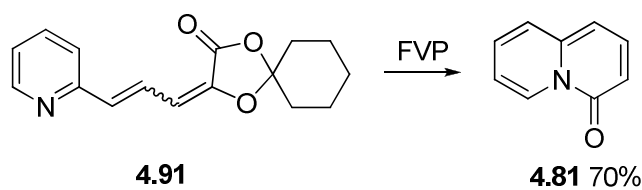
Scheme 4.47 Synthesis of dioxolane fragment **4.92**

Using the literature conditions for Wittig reactions with the phosphonium salt⁸⁵ (DABCO, toluene), the desired product **4.91** was isolated in 19% yield after purification by column chromatography (Scheme 4.48) as a mixture of stereoisomers which were not separated.



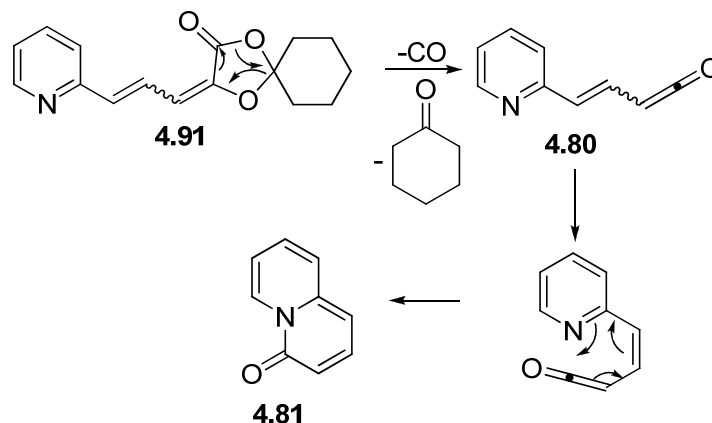
Scheme 4.48 Synthesis of compound **4.91**

With the pyrolysis precursor at hand, the FVP experiment was carried out at 600 °C. Two products could be seen to be forming: a brown solid forming at the Quickfit joint and a clear oil forming at the bend of the U-tube, along with an increase in pressure. The ^1H NMR spectrum of the crude pyrolysate confirmed the presence of the quinolizinone product by comparison with the literature spectrum.⁸⁷ Column chromatography, to remove the cyclohexanone, gave quinolizinone **4.81** in 70% yield (Scheme 4.49).



Scheme 4.49 Pyrolysis of compound **4.91**

The mechanism for the pyrolysis proceeds by retro-electrocyclisation, with loss of carbon monoxide and cyclohexanone, to give the pyridylketene **4.80**. The geometry of the double bond does not matter due to the possibility of isomerisation of alkenes under FVP conditions (see chapter 1, page 12). This then goes through the pseudopericyclic cyclisation to give quinolizinone **4.81** (Scheme 4.50)



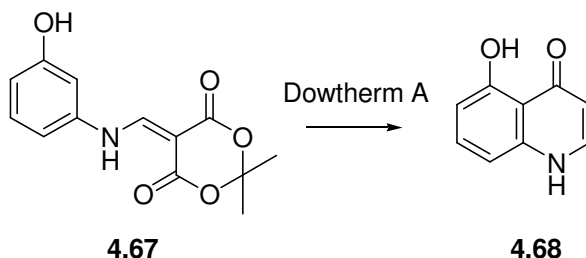
Scheme 4.50 Mechanism of the pyrolysis of compound **4.91**

This methodology provides an alternative route to quinolizinones, but requires some improvements, particularly with the purification of the phosphonium salt.

4.2.4 Solution-Phase Pyrolysis

Although quinolinones can be synthesised by FVP, such reactions are often performed in solution phase using high-boiling solvents such as Dowtherm A. As discussed in previous chapters, the amount of deuterium exchange observed in solution phase pyrolysis of anilino methylene Meldrum's acid compounds differs from that observed in FVP experiments. This can be attributed to the possibility of intermolecular processes, by-passing the 1,5-hydrogen shift.

Solution-phase pyrolysis of compound **4.67** gave a brown solid, which when dissolved in d_6 -DMSO showed one major product with minor impurities. The major compound was identified as 5-hydroxyquinolinone **4.68** by comparison with the ^1H NMR data of a known sample. There were no resonances in the spectrum that could be assigned to 8-hydroxyquinolizinone **4.69** (Scheme 4.51).



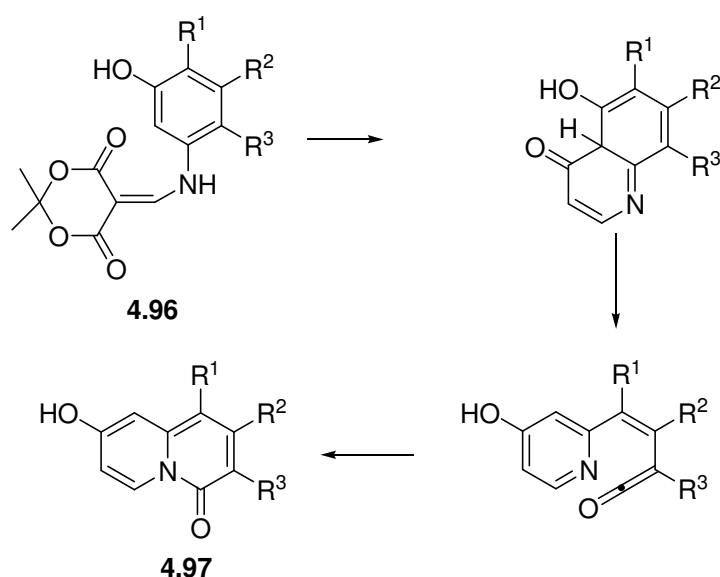
Scheme 4.51 Solution phase pyrolysis of compound **4.67**

From this, it can be said that the solution-phase pyrolysis leads to the formation of the thermodynamic product, with no ability to control the reaction, while in the gas phase control of the furnace temperature can give both the kinetic and thermodynamic products under appropriate conditions.

4.2.5 Scope of Reaction

4.2.5.1 Substitution on Aminophenol

With the mechanism for the reaction determined, the scope of the rearrangement was explored. The first area to investigate was the substitution on the aminophenol ring. With the appropriate substituted aminophenol precursor **4.96**, substitution in the 1, 2 or 3-positions of the quinolizinone ring (compound **4.97**) can be achieved (Scheme 4.52).



Scheme 4.52 Pyrolysis of substituted precursor **4.96**

From a range of substituted 3-aminophenols, two were commercially available (methyl and methoxy compounds **4.98** and **4.99**), while another two (compounds **4.100** and **4.101**) were available in one step from commercially available starting materials (Figure 4.11).

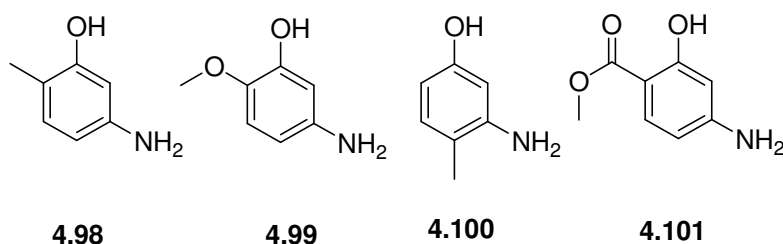
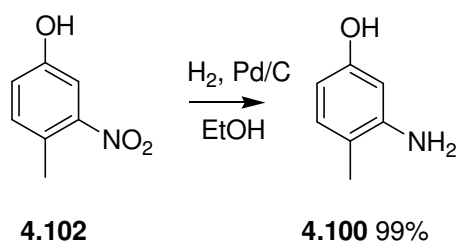


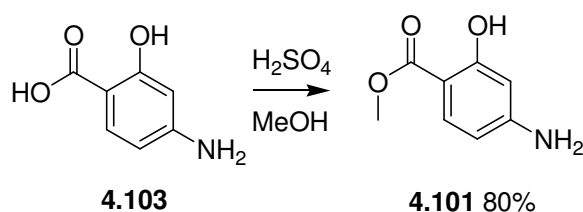
Figure 4.11 Chosen substituted 3-aminophenols

5-Amino-*p*-cresol **4.100** was synthesised by hydrogenation of the corresponding nitro compound **4.102**, using palladium on carbon in 99% yield (Scheme 4.53).



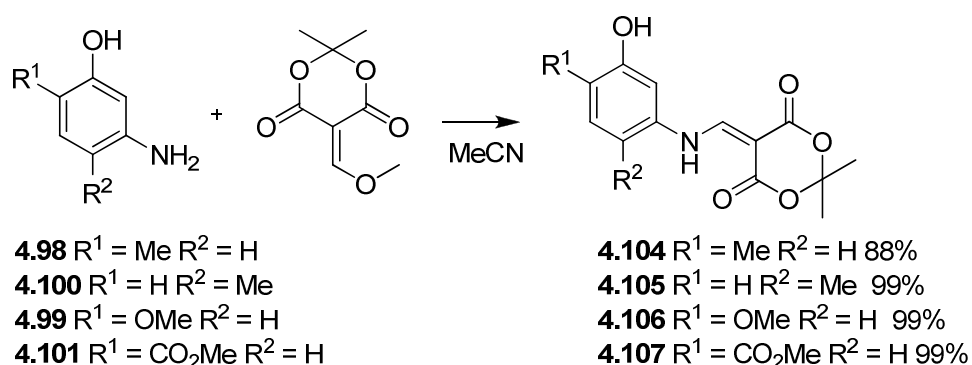
Scheme 4.53 Synthesis of compound **4.100**

Esterification of 4-aminosalicylic acid **4.103**, using methanol and sulfuric acid, gave the required ester **4.101** in 80% yield after work-up (Scheme 4.54).



Scheme 4.54 Synthesis of compound **4.101**

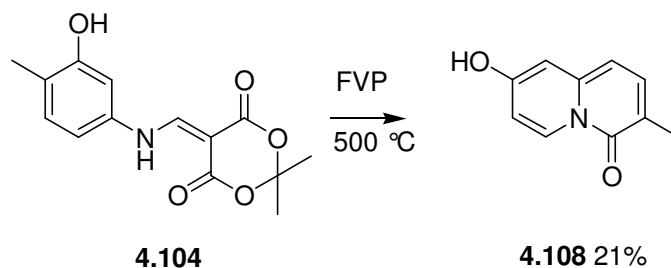
With the required aminophenols at hand, the compounds were reacted with methoxymethylene Meldrum's acid under the standard conditions to give compounds **4.104** – **4.107** (Scheme 4.55).



Scheme 4.55 Synthesis of pyrolysis precursors **4.104** – **4.107**

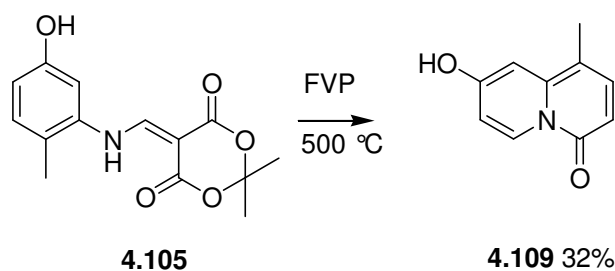
With the desired precursors synthesised, the pyrolysis experiments were performed. Pyrolysis of methyl compound **4.104** gave a yellow solid, which was a mixture of 3-

methyl-8-hydroxyquinolizinone **4.108** and 5-hydroxy-6-methylquinolinone in a 9:2 ratio. Recrystallisation of the solid from DMF gave the quinolizinone **4.108** in 21% yield (Scheme 4.56).



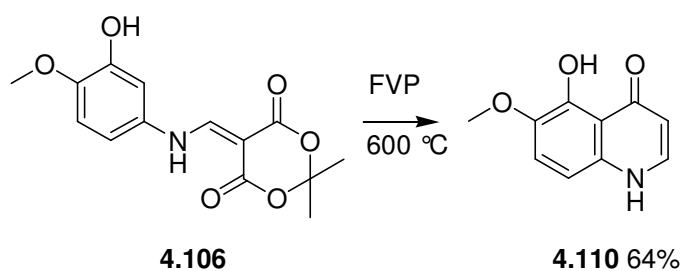
Scheme 4.56 Pyrolysis of compound **4.104**

Similarly pyrolysis of methyl compound **4.105** also gave a yellow solid, which was mainly 8-hydroxy-1-methylquinolizinone **4.109**, with 5-hydroxy-8-methylquinolinone in a 5:1 ratio. Heating the solid in methanol was sufficient to remove the quinolinone by product, giving quinolizinone **4.109** in 32% yield (Scheme 4.57).



Scheme 4.57 Pyrolysis of compound **4.105**

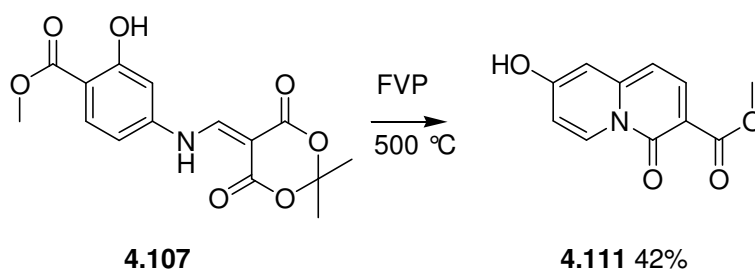
Pyrolysis of the methoxy compound **4.106**, however gave only a trace amount of the 8-hydroxy-8-methoxyquinolizinone at 500 °C. The major product isolated was 5-hydroxy-6-methoxyquinolinone **4.110**, which at 600 °C, was isolated in 64% yield (Scheme 4.58).



Scheme 4.58 Pyrolysis of compound 4.110

The methyl ester **4.107** was highly involatile and significant decomposition occurred in the inlet tube. In addition, the product condensed at the exit point of the furnace tube and U-tube and began to decompose due to the proximity of the high temperature zone. To overcome this, a diffusion pump was employed. This allows for lower pressures to be reached, which lowers the inlet temperatures required and should minimise the amount of decomposition.

With the diffusion pump, the amount of decomposition of the precursor was decreased significantly but the product still formed at the exit point of the furnace tube. It was possible to separate a yellow solid from the decomposed black material and methyl 8-hydroxyquinolizinone-3-carboxylate **4.111** was isolated in 42% yield (Scheme 4.59)



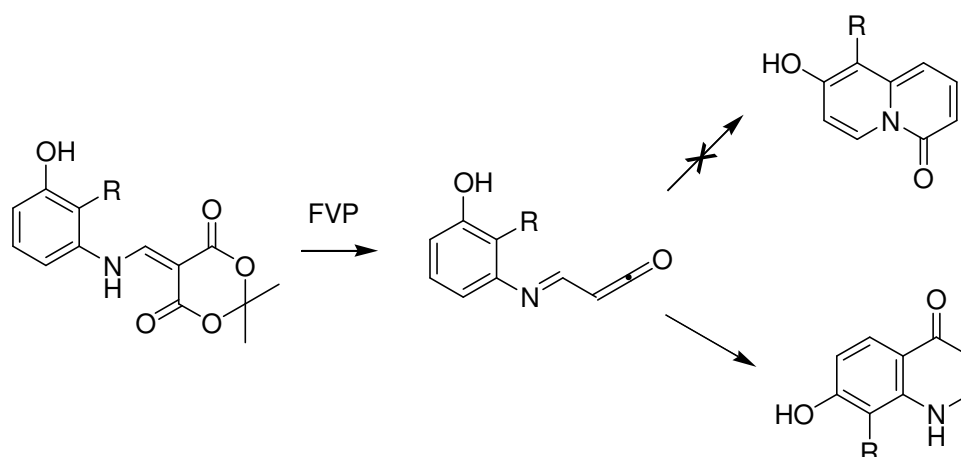
Scheme 4.59 Pyrolysis of compound 4.107

In this pyrolysis, none of the quinolinone product was observed at 500 °C, unlike the other substituted 3-aminophenols.

The results of the pyrolysis appear to be dependent on the substituent. In all cases, none of the 7-substituted quinolinones were observed, so the electrocyclisation step is still regioselective for the 5-hydroxyquinolinone. However the more electron donating substituents gave less of the quinolizinone products than the electron withdrawing ester substituent.

Substitution in the 2-position of the aniline might not be expected to give the quinolizinone product, acting as a block to the *ortho*-cyclisation and therefore might

give only the 7-substituted quinolinone (Scheme 4.60).



Scheme 4.60 Proposed pyrolysis experiment

To test the feasibility of the reaction, DFT calculations at B3LYP/6-31G** level were used to model the energy surface of the reaction. Since 3-amino-*o*-cresol was easily synthesised, the R group in scheme 4.60 was set to a methyl group for the purposes of the calculation. The calculated energy surface is shown below (Figure 4.12).

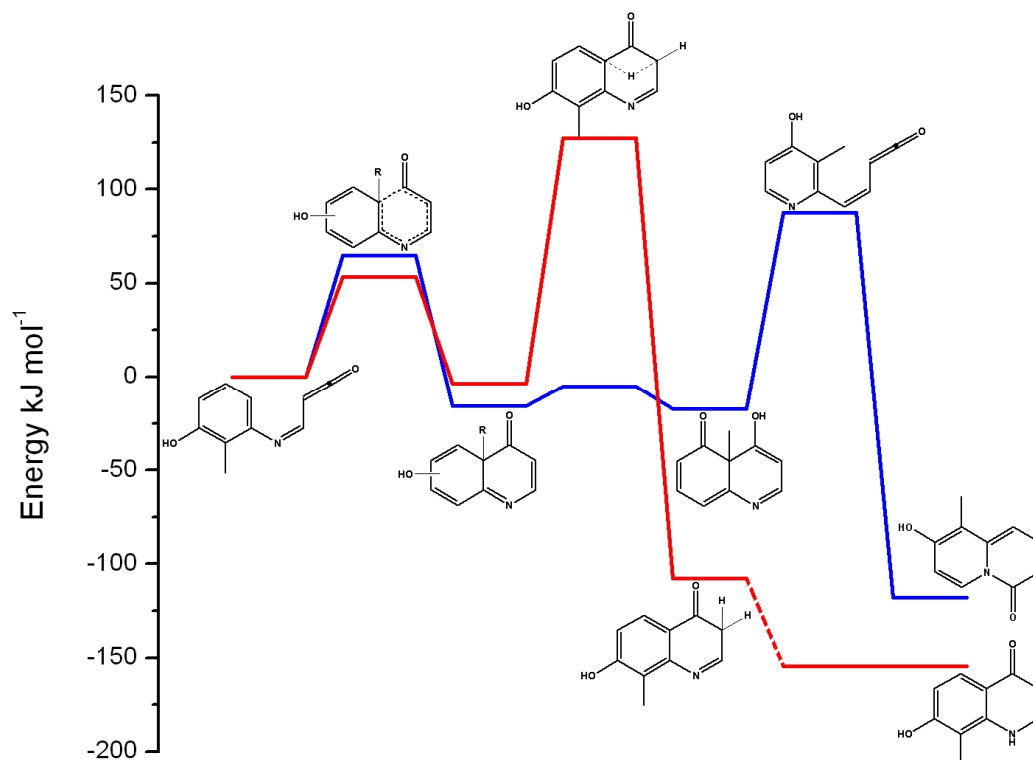
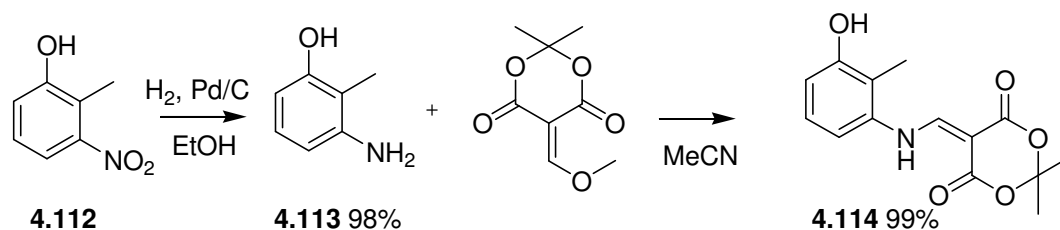


Figure 4.12 Energy surface for the pyrolysis of the 2-methyl-3-aminophenol derived compound

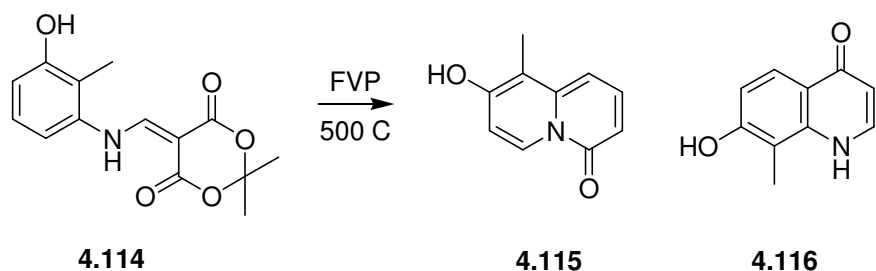
From figure 4.12, although the barrier to the initial cyclisation is higher than that of the corresponding 7-substituted product, the hydrogen transfer step leading to the formation of the quinolizinone is still much lower in energy. Based on the energy surface, the pyrolysis should give the quinolizinone product, perhaps with traces of the 7-hydroxyquinolinone.

The precursor for the pyrolysis was synthesised starting from 3-nitro-*o*-cresol **4.112**, which was hydrogenated using palladium on carbon to give 3-amino-*o*-cresol **4.113** in 98% yield. Reaction with methoxymethylene Meldrum's acid gave compound **4.114** in excellent yield (Scheme 4.61)



Scheme 4.61 Synthesis of the pyrolysis precursor **4.114**

With the desired precursor synthesised, the pyrolysis was carried out at 500 °C. The pyrolysis gave a yellow solid, isolated in 70% yield from the U-tube trap. The crude ^1H NMR spectrum of the product showed a mixture of two products in a 4:1 ratio. The major product was identified as the 8-hydroxy-9-methylquinolizinone **4.115** by the presence of 5 methine protons in the ^1H NMR spectrum and in particular the doublet at $\delta_{\text{H}} = 9.0$ ppm. The minor product showed 4 doublets in the ^1H NMR spectrum, typical of the expected product, 7-hydroxy-8-methylquinolinone **4.116** (Scheme 4.62)

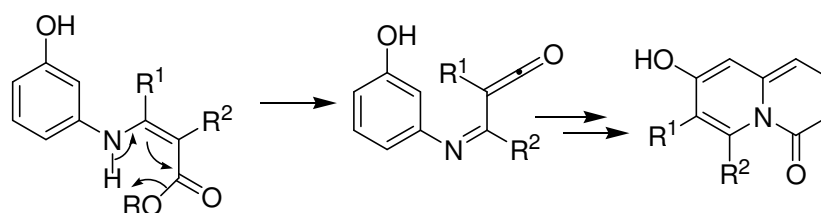


Scheme 4.62 Pyrolysis of compound **4.114**

Attempts to separate the two products by column chromatography failed due to the instability of the quinolizinone on silica. However the result shows that the hydrogen bonding interaction between the hydroxy- hydrogen atom and the ketene (which directs the reaction towards the 5-position) is strong enough to overcome any steric effects of the *ipso* cyclisation.

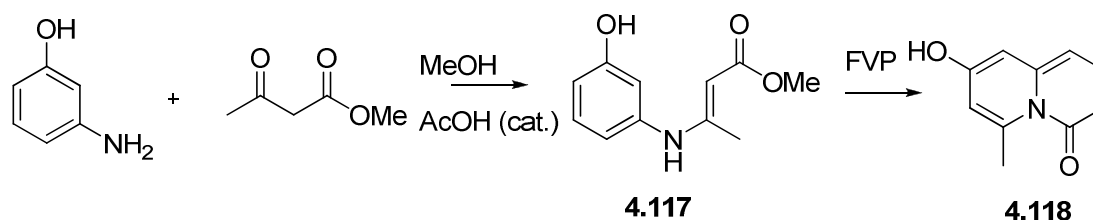
4.2.5.2 Alternative Ketene Generators

It is known that FVP of acrylate esters can lead to generation of ketenes, with loss of the alcohol from the ester.¹¹ Therefore precursors based on acrylate esters were employed as an alternative ketene generator. These would provide potential for substitution in the 6- and 7- positions of the quinolizinone ring (Scheme 4.63)



Scheme 4.63 Pyrolysis of acrylate ester

Condensation of 3-aminophenol with methyl acetoacetate, should give compound **4.117**. Pyrolysis of this compound should then lead to the formation of 8-hydroxy-6-methylquinolizinone **4.118** (Scheme 4.64)



Scheme 4.64 Proposed synthesis of 8-hydroxy-6-methylquinolizinone

Heating 3-aminophenol and methyl acetoacetate in methanol with a catalytic amount of acetic acid gave the desired compound. The reaction, however, required some optimisation. Removing the unreacted 3-aminophenol proved difficult, with

recrystallisation only providing 3-aminophenol and not the product. Washing the reaction mixture with copper sulfate was found to be effective in removing the 3-aminophenol, most likely by chelation of the 3-aminophenol to the copper. If an excess of acid is added, then reaction proceeds *via* a known acid-catalysed reaction to give 7-amino-4-methylcoumarin.¹¹¹

Pyrolysis of compound **4.117** at 500 °C lead to the formation of a brown solid and inspection of the ¹H NMR spectrum showed the expected quinolizinsonone, starting material and quinolinones in a 78:11:11 ratio. Since the ketene generator has changed, the optimum temperature might also change. To determine the optimum temperature, a temperature profile was obtained of the reaction (Figure **4.13**)

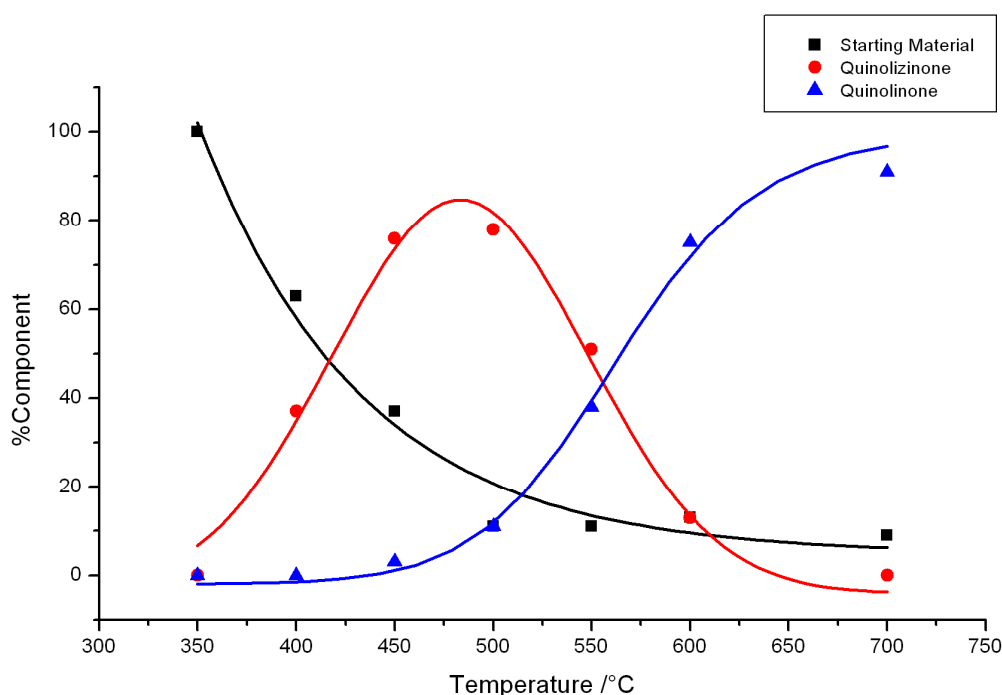
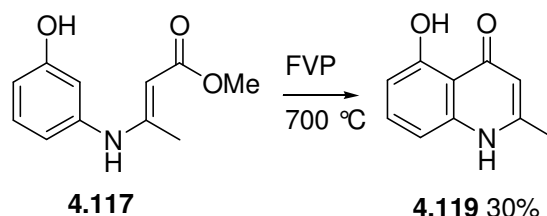


Figure 4.13 Temperature profile for the pyrolysis of compound **4.117**

From figure **4.13**, the optimal temperature was found to be 450 °C. The reason for choosing this temperature over 500 °C is due to the difficulty in removing the quinolinone. At 500 °C, the 10% of quinolinone obtained could potentially be difficult to remove due to its similar solubility to the quinolizinsonone. At 450 °C, the amount of quinolinone **4.119** is insignificant and the increased amount of starting

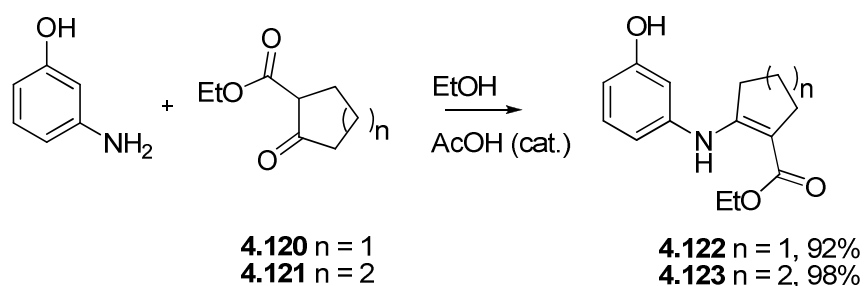
material is easily removed, due to its high solubility relative to the quinolizinone. At 700 °C, 5-hydroxy-2-methylquinolinone **4.119** is obtained, isolated in 30% yield after purification (Scheme 4.65).



Scheme 4.65 Pyrolysis of compound **4.117** to give quinolinone **4.119**

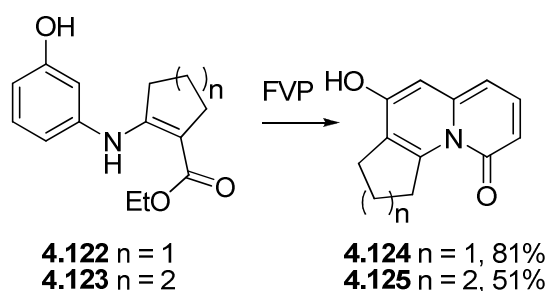
The ^1H NMR spectrum of 8-hydroxy-6-methylquinolizinone **4.118** has some interesting features. Since the methyl group is now in the deshielding zone of the carbonyl group, it experiences a high frequency shift to $\delta_H = 2.94$ ppm. In comparison the methyl groups of 1-methyl- and 3-methyl-hydroxyquinolizinones have chemical shifts of $\delta_H = 2.21$ and $\delta_H = 2.12$ ppm respectively.

This methodology was extended, by replacing methyl acetoacetate with ethyl 2-oxocyclopentanecarboxylate **4.120** and ethyl 2-oxocyclohexanecarboxylate **4.121**, to give compounds **4.122** and **4.123** in excellent (>90%) yields (Scheme 4.66)



Scheme 4.66 Synthesis of compounds **4.122** and **4.123**

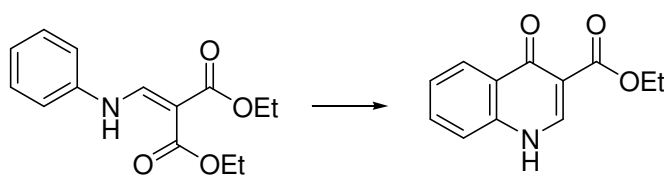
Pyrolysis of compounds **4.122** and **4.123** gave brown solids, which when subjected to the same purification process as for the methyl example, gave the fused ring quinolizinones **4.124** and **4.125** (Scheme 4.67)



Scheme 4.67 Pyrolysis of compounds **4.122** and **4.123**

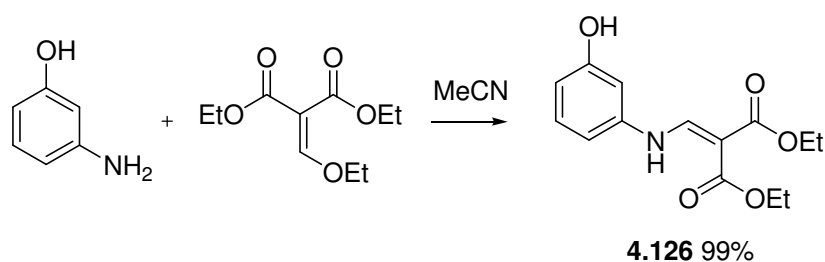
Both of these compounds show the same high frequency shift in the ^1H NMR spectra, due to one of the CH_2 groups being in the deshielding zone of the carbonyl group, as was observed with the 6-methyl analogue **4.118**.

The reaction of anilines and diethyl ethoxymethylenemalonate is used to synthesise precursors for the synthesis of quinolinone-3-carboxylates (Scheme **4.68**).



Scheme 4.68 Synthesis of ethyl quinolinone-3-carboxylate

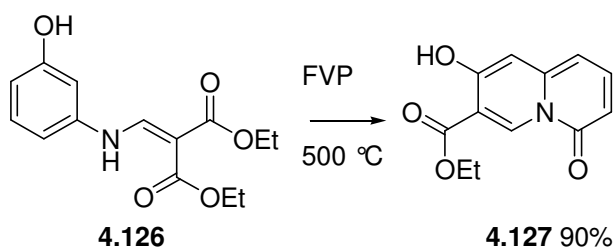
Using this reaction with 3-aminophenol gave compound **4.126** in excellent yield (Scheme **4.69**).



Scheme 4.69 Synthesis of compound **4.126**

Upon pyrolysis of compound **4.126** at 500 °C, a yellow-orange solid was formed at the exit point of the furnace. Dissolution of the compound in chloroform-*d* showed the presence of a single product, with a singlet in the ^1H NMR spectrum at $\delta_{\text{H}} = 9.6$

ppm. The product formed from the reaction is 7-carboethoxy-8-hydroxyquinolizinone **4.127**, in 90% yield (Scheme 4.70)



Scheme 4.70 Pyrolysis of compound **4.126**

The pyrolysis to form compound **4.127** was found to be highly scalable, with no or minimal loss of yield using 10 g of precursor.

An X-ray crystal structure of compound **4.127** was obtained (Figure 4.14)

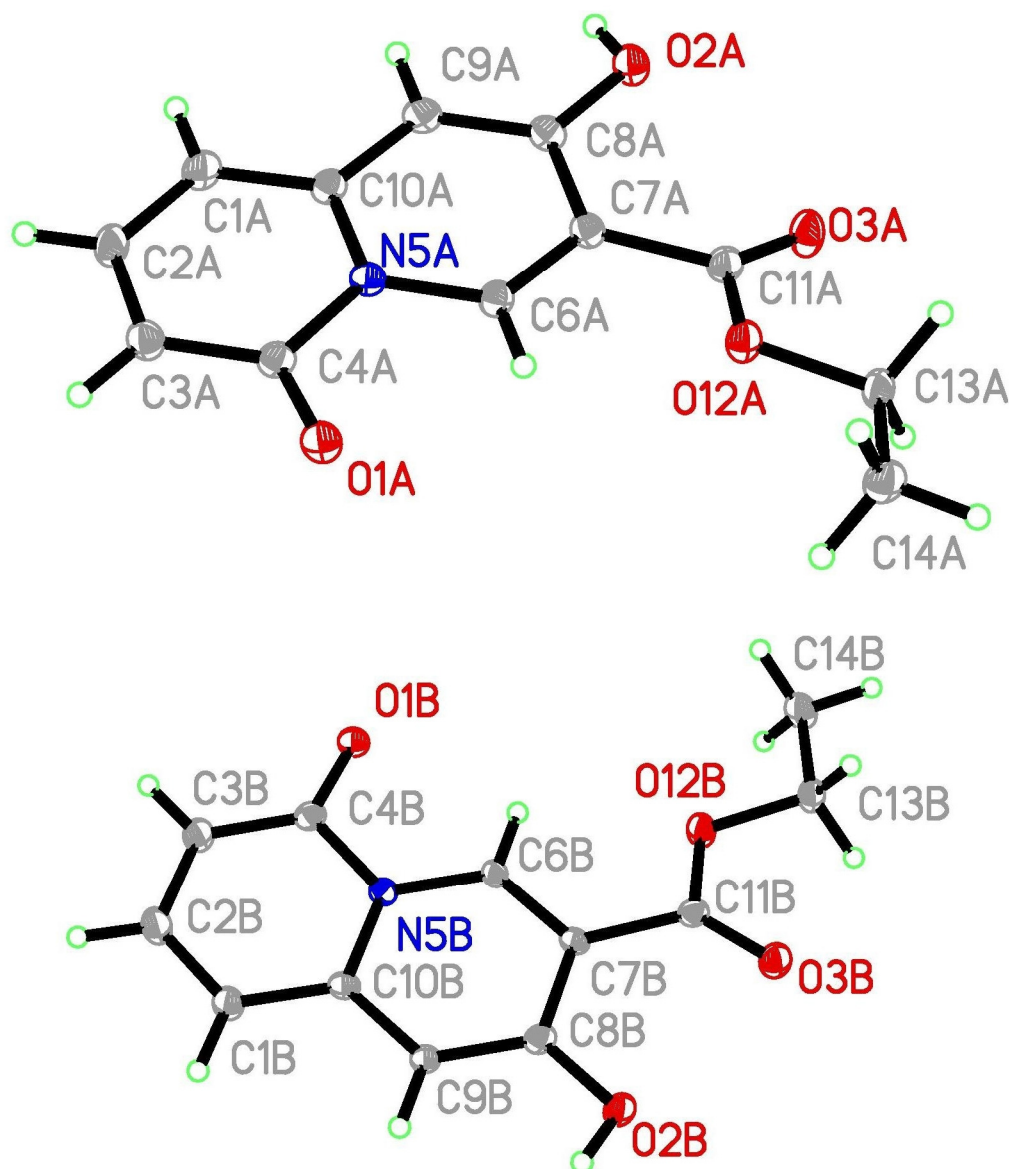


Figure 4.14 Crystal structure of compound **4.127**, with 2 independent molecules in the unit cell.

The structure shows two molecules per unit cell stacked above one another. There appears to be no obvious interactions, such as hydrogen bonding or π stacking, between the molecules. In solution phase, the hydroxy- hydrogen atom is observed at $\delta_H = 10.69$ ppm in the ^1H NMR spectrum, hinting at hydrogen bonding in the solution phase. The crystal structure confirms that the quinolizinone ring system is indeed formed in these reactions.

A comparison of the crystal structure of compound **4.127** with the reported crystal

structure⁶⁶ of compound **4.25** (Figure 4.15) shows a number of features (Table 4.3)

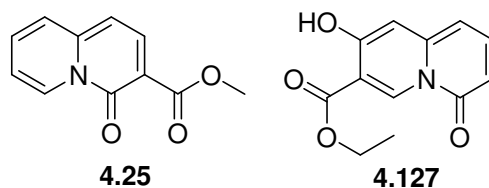


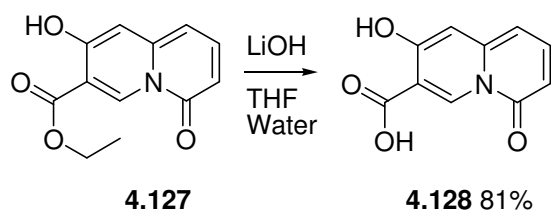
Figure 4.15 Structures of compounds **4.25** and **4.127**

Bond	Compound 4.25	Compound 4.127
C1-C2	1.360	1.377(4)
C2-C3	1.398	1.382(4)
C3-C4	1.413	1.388(4)
C4-N5	1.466	1.432(3)
N5-C6	1.380	1.372(4)
C6-C7	1.341	1.364(3)
C7-C8	1.398	1.442(3)
C8-C9	1.348	1.371(4)
C9-C10	1.415	1.401(4)
C10-C1	1.382	1.388(4)
C4-O1	1.225	1.251(3)
N5-C10	1.384	1.400(3)

Table 4.3 Bond lengths for the quinolizinone ring system of compounds **4.25** and **4.127**

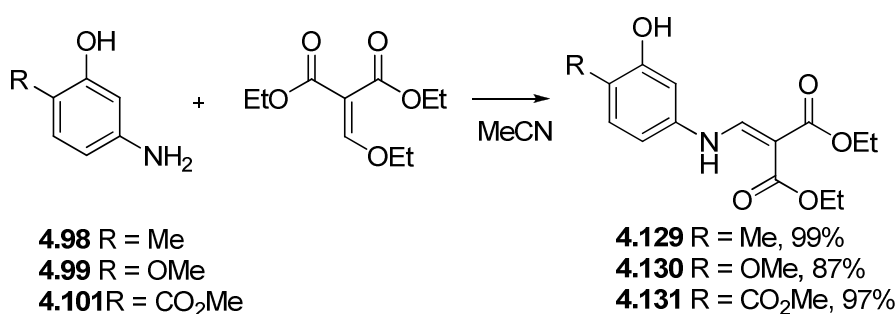
Only one ESD value for crystal structure of compound **4.25** was quoted in the paper⁶⁶ (0.002), indicating that the other bond lengths may possess similar ESD values. There are a number of differences between the bond lengths of compound **4.25** and **4.127**. In particular the C4 carbonyl bond is longer in compound **4.127** than in compound **4.25**, as is the C7-C8 bond. In compound **4.127**, most of the bonds in the left ring are longer, while most of bonds in right hand ring are shorter.

Compound **4.127** could be hydrolysed to give the 7-carboxylic acid **4.128**, using lithium hydroxide in THF and water, in 81% yield (Scheme 4.71).



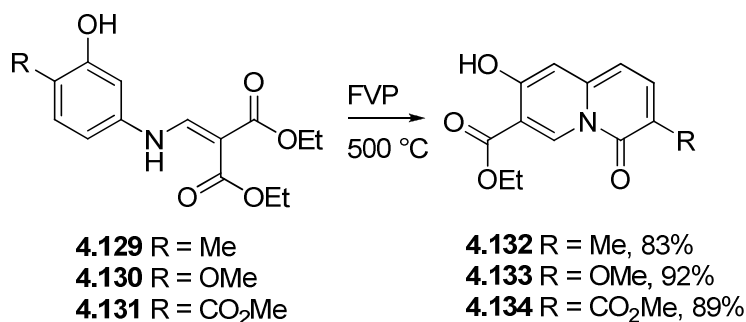
Scheme 4.71 De-esterification of compound **4.127**

Starting from substituted aminophenols **4.98**, **4.99** and **4.101**, compounds **4.129**, **4.130** and **4.131** were synthesised in a similar fashion to compound **4.126** (Scheme 4.72)



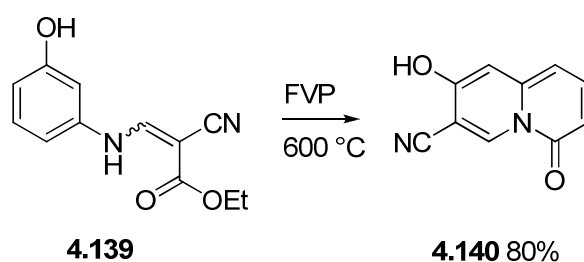
Scheme 4.72 Synthesis of substituted compounds **4.129** – **4.131**

Pyrolysis of compounds **4.129** – **4.131** at 500 °C gave orange-red solids, which were chloroform-soluble, in 80 – 90% yields. The ¹H NMR spectra showed the formation of the quinolizinoquinones **4.132** – **4.134**, identifiable by the characteristic singlet at δ_H = 9.6 – 10.0 ppm (Scheme 4.73)



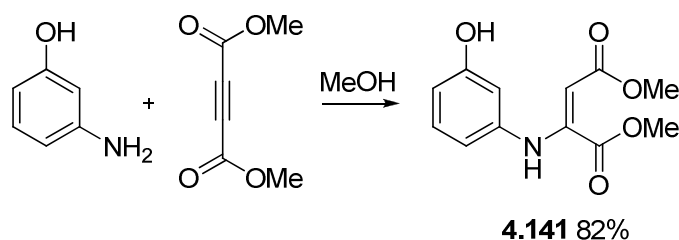
Scheme 4.73 Pyrolysis of compounds **4.129** – **4.131**

Of interest is the higher overall yields than the corresponding Meldrum's acid derivatives and the fact that methoxy example **4.130**, which failed to yield the



Scheme 4.76 Pyrolysis of compound **4.139**

Dimethyl acetylenedicarboxylate (DMAD) has been used as a Michael acceptor for anilines, and pyrolysis of the products leads to the formation of quinolinones with an ester in the 2-position.¹¹ Addition of DMAD to 3-aminophenol in methanol led to the formation of an orange oil, which could be purified by column chromatography to give the product **4.141** (Scheme 4.77)

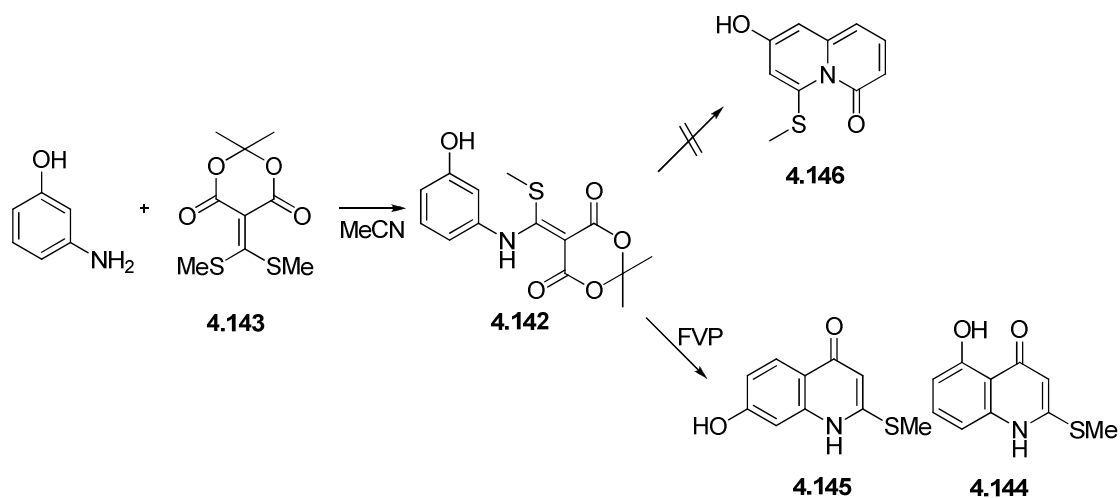


Scheme 4.77 Synthesis of compound **4.141**

Pyrolysis of compound **4.141** led to the formation of a brown solid at the exit point of the furnace, as expected with quinolizinones. However the ^1H NMR spectrum of the crude material showed a complex mixture, with no identifiable peaks that could be assigned to the starting material or either of the two expected products.

Another potential route to 6-substituted quinolizinones involves the pyrolysis of compound **4.142**, which was synthesised from bis(thiomethyl)methylene Meldrum's acid **4.143** and 3-aminophenol in 62% yield after recrystallisation. Pyrolysis of compound **4.142** led to the formation of a yellow solid, formed at the exit point of the furnace. The ^1H NMR spectrum in d_6 -DMSO of the crude material, however showed the presence of two compounds, in a 4:1 ratio. Both products showed the presence of 4 aromatic protons and 1 methyl group, indicating that only the 5- and 7-hydroxyquinolinones **4.144** and **4.145** had been formed and none of the quinolizinone

4.146 was observed (Scheme **4.78**).



Scheme 4.78 Pyrolysis of compound **4.142**

The major isomer showed two doublet, one triplet and a singlet, which identifies it as the 5-hydroxyl isomer. The minor isomer showed the presence of two doublets and two singlets, consistent with the 7-hydroxyl isomer.

DFT calculations were employed to model the energy surface for the thiomethyl reaction (Figure **4.16**)

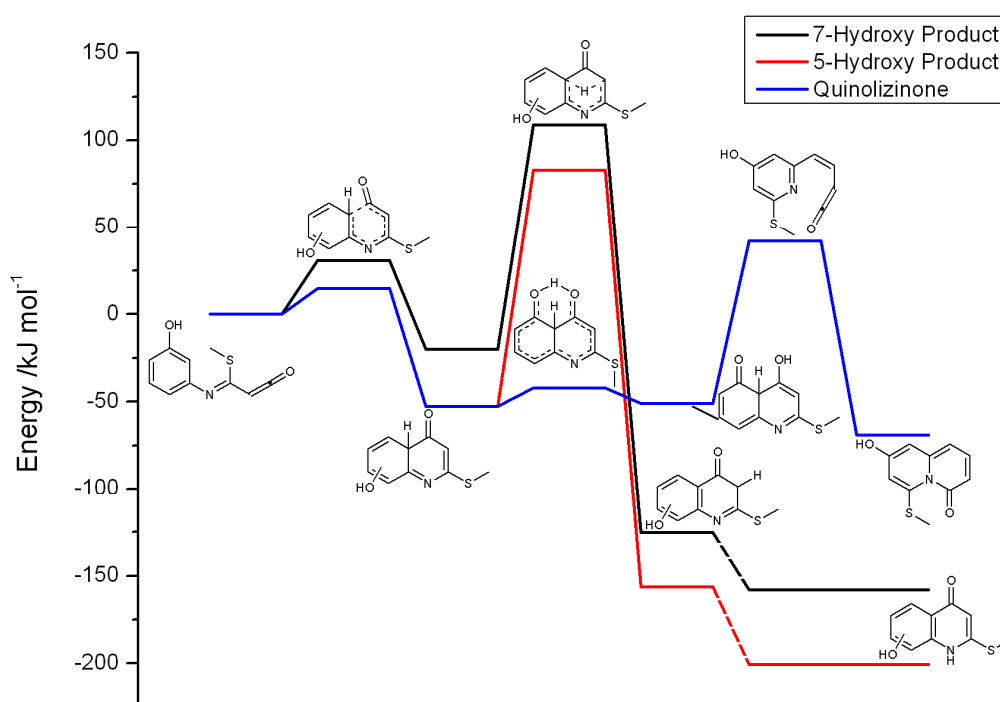


Figure 4.16 Energy Surface for the formation of compounds **4.144** – **4.146**

From figure **4.16**, the reason why the quinolizone does not form becomes apparent. The energy of the quinolizone product is much higher in energy than it was for the unsubstituted example. This higher energy is most likely due to the peri-interaction between the thiomethyl and carbonyl groups in the molecule. Once the quinolizone is formed, it has sufficient energy to undergo the reverse reaction and reform the intermediate to undergo the 1,5 hydrogen shift (to give the quinolinone product). However the calculations do not explain why the 7-isomer is observed in the reaction.

In conclusion, the scope of the cyclisation reaction to form 8-hydroxyquinolizinones has been explored. Firstly substitution on the aminophenol ring is tolerated to an extent, with electron-withdrawing substituents giving better results than electron-donating groups. Secondly alternative ketene generators, such as acrylate esters, can also be used to synthesise 8-hydroxyquinolizinones. Precursors that lead to substitution in the 7-position give high yields of quinolizinones. Precursors that place groups in the 6-position do not give as high yields, most likely due to peri-interactions between the group and the carbonyl in the 4-position, but can be used to give 6-substituted quinolizinones in most examples.

Overall, this work is the best route to 8-hydroxyquinolizinones to date. The yields range from moderate to excellent, based on the substitution pattern required. In general, the quinolizinones can be obtained in 2 steps from 3-aminophenol and the precursors are easily synthesised. The reaction avoids the use of strong bases typically used in the synthesis of quinolizinones and no unwanted ester groups typically required for the formation of quinolizinones are left on the quinolizinone ring system.

4.2.6 Extension to Benzoquinolizinones

Under the author's supervision, a final year project was undertaken to attempt to synthesise benzoquinolizinones.⁸⁸ The work was performed by Ms. Katarzyna Werecka. The DFT calculations for the reactions were performed by the author at B3LYP/6-31G** level.

The desired precursor for the proposed pyrolysis was based on *N*-phenylanthranilic acid. However under FVP conditions, esters are often preferred to acids, as the reactions tend to be cleaner and the precursors more volatile. While both the acid and ester of *N*-phenylanthranilic acid **4.147** were available, literature routes were only known for the acid of hydroxy- compound **4.148** (Figure 4.17).

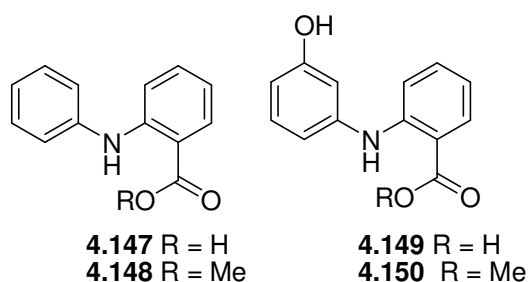
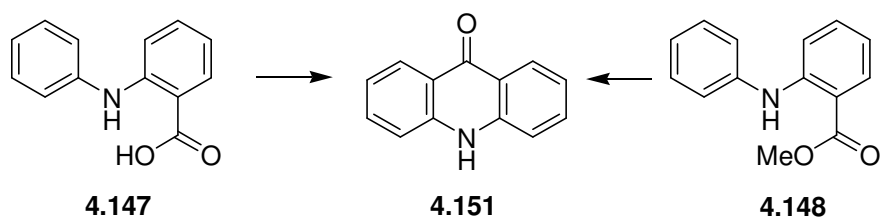


Figure 4.17 Pyrolysis precursors **4.147** – **4.150**

The first experiment was to compare the temperature profiles of the pyrolysis of *N*-phenylanthranilic acid **4.147** and its methyl ester **4.148** (Scheme 4.79), and observe if the acid is suitable for synthesising acridinones under FVP conditions.



Scheme 4.79 Synthesis of acridinone **4.151**

The temperature profiles for the two pyrolysis experiments are shown below (Figure 4.18).

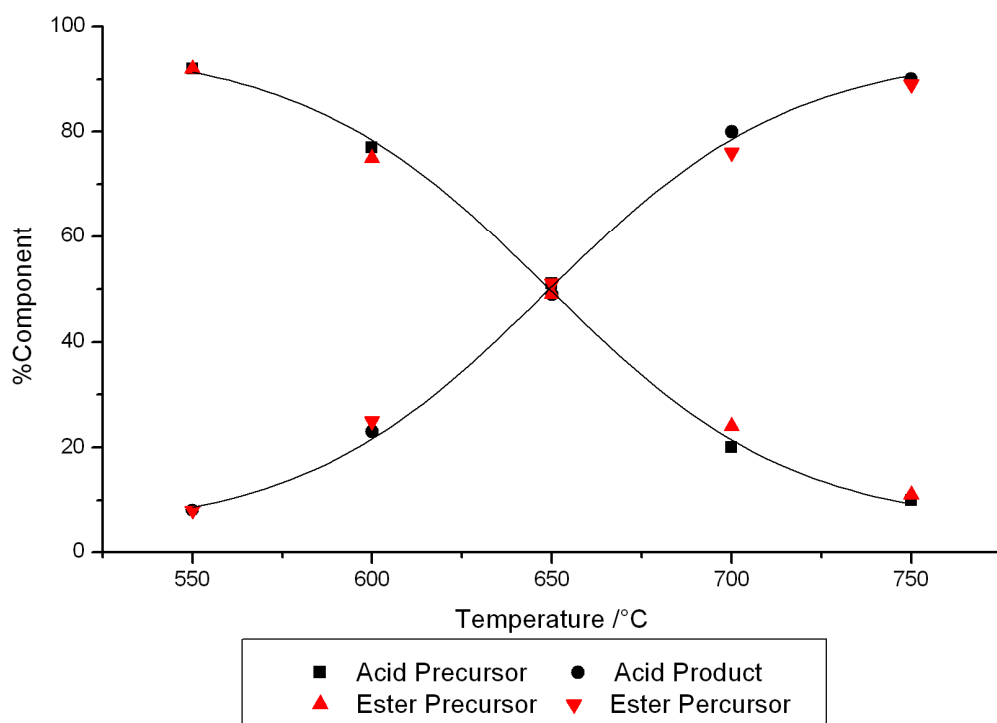
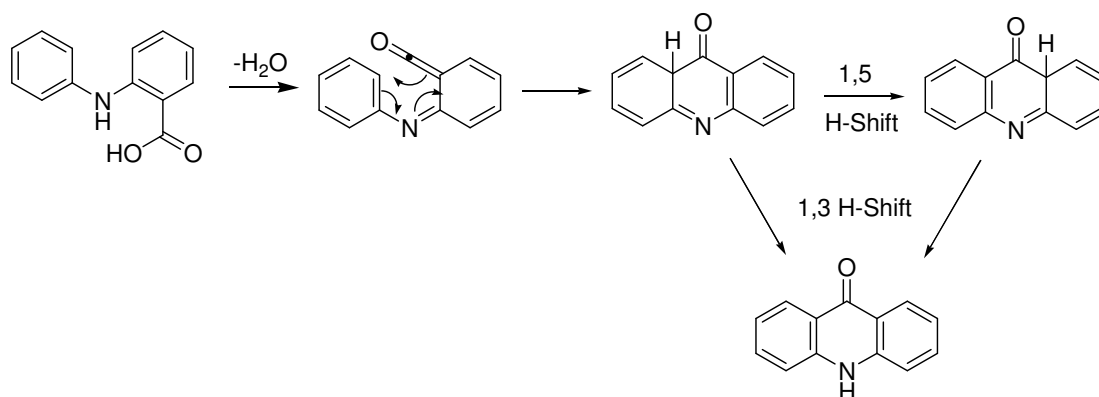


Figure 4.18 Temperature profile of ester **4.147** against acid **4.148**

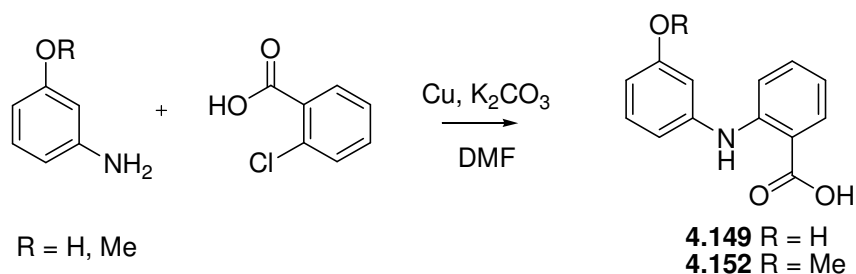
From figure 4.18, there are no observable differences between the two precursors in their temperature profiles. The temperatures required for the acridinone formation are significantly higher than those required for the formation of quinolinones from either the Meldrum's acid or acrylate ester precursors. From this, the acid precursors were chosen due to the literature precedent on their synthesis. The mechanism is similar to that of the acrylate esters (Scheme 4.80).



Scheme 4.80 Mechanism of the formation of the acridinone **4.151**

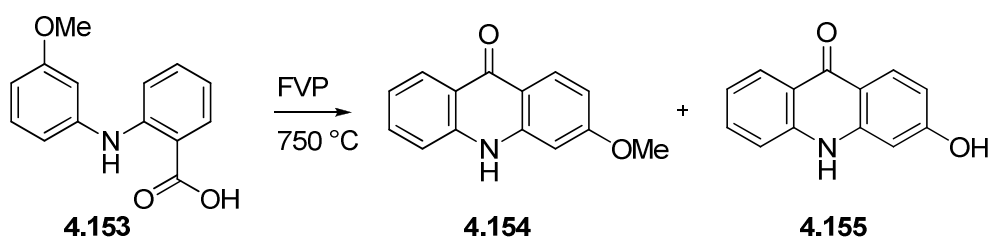
The mechanism also reveals why the furnace temperatures required are higher than for acrylate ester precursors. The initial formation of the imidoylketene breaks the aromaticity of the benzene ring, which would require much more energy than it does to initiate loss of the alcohol.

This work was further extended to *meta*-substituted compounds, using a methoxy and a hydroxy- substituent. The precursors were synthesised using an Ullman coupling of *meta*-substituted aniline with 2-chlorobenzoic acid (Scheme **4.81**)



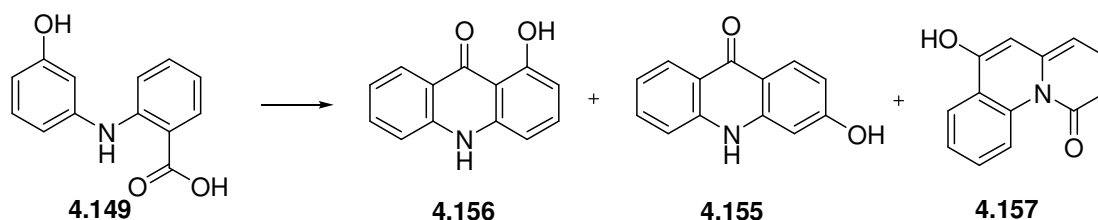
Scheme 4.81 Synthesis of pyrolysis precursors **4.149** and **4.152**

Pyrolysis of the methoxy- compound **4.153** at 750 °C gave 3-methoxyacridinone **4.154**, with amounts of 3-hydroxyacridinone **4.155** (Scheme **4.82**). The cyclisation was found to occur exclusively *para* to the substituent, similar to that of the quinolinone example (see chapter 3).



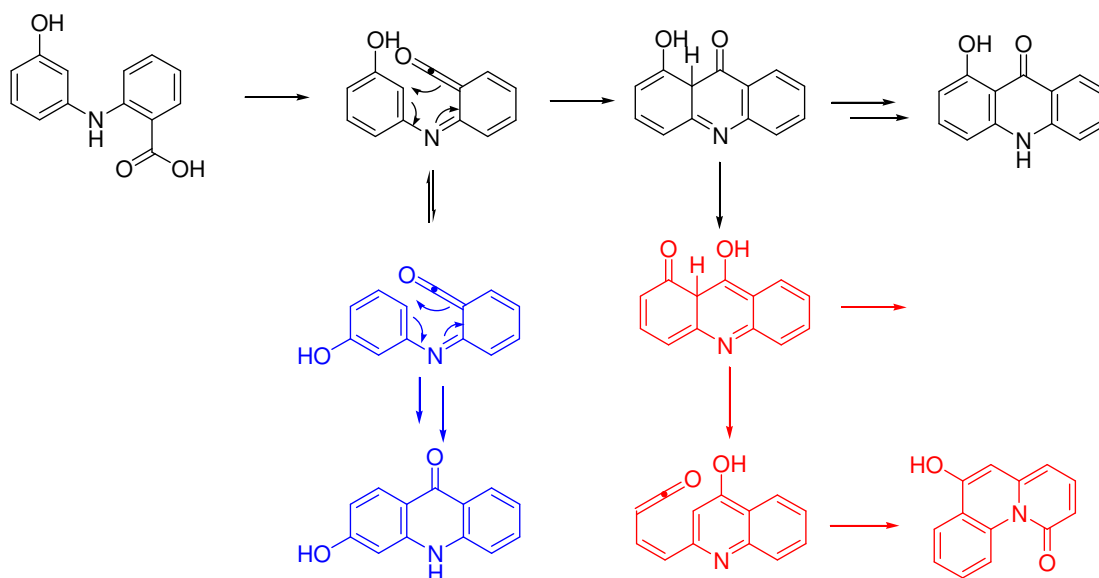
Scheme 4.82 Pyrolysis of compound **4.153**

Pyrolysis of the 3-aminophenol derived precursor **4.149** resulted in the formation of three products. These were identified as 1-hydroxyacridinone **4.156**, 3-hydroxyacridinone **4.155** and hydroxybenzoquinolizinone **4.157** (Scheme 4.83).



Scheme 4.83 Pyrolysis of compound **4.149**

The mechanism of the reaction is analogous to the mechanism for the formation of the hydroxyquinolinones and hydroxyquinolizinones (Scheme 4.84)



Scheme 4.84 Mechanism for the pyrolysis of compound **4.149**

The temperature profile for the pyrolysis is shown below (figure 4.19)

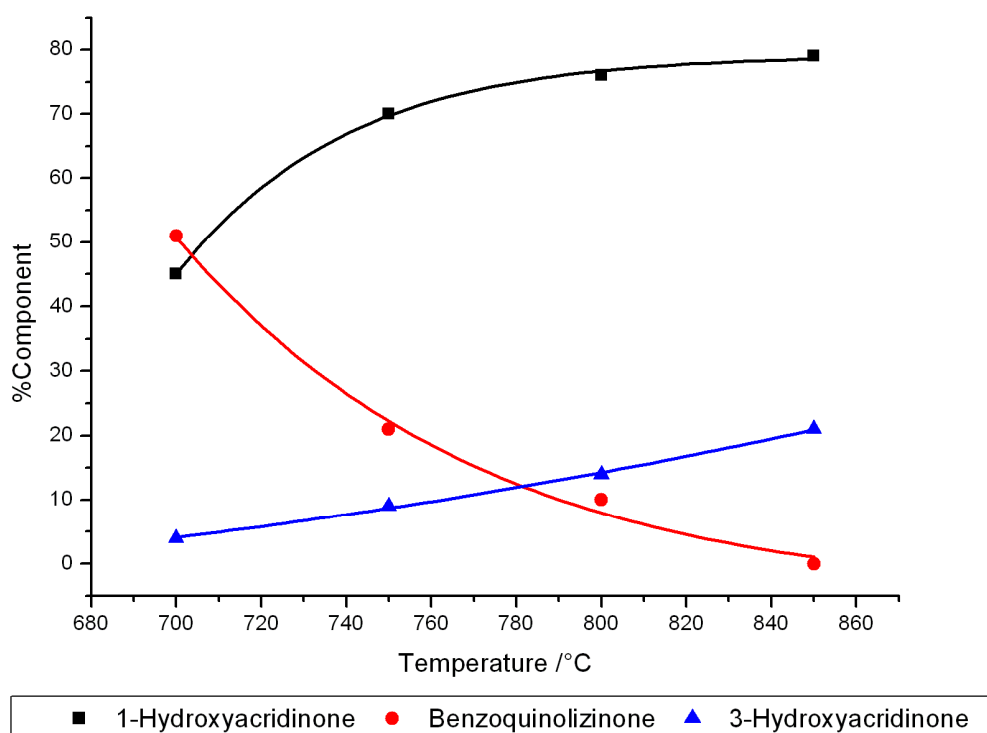


Figure 4.19 Temperature profile for the pyrolysis of compound **4.149**

The maximum amount of benzoquinolizininone **4.157** obtained in the pyrolysis was 51%, at 700 °C. At lower furnace temperatures, significant amounts of starting material would further complicate the reaction mixtures. The other major product was 1-hydroxyacridinone **4.156**.

The energy surface obtained of the two hydroxyacridinones is shown in figure **4.20** (below)

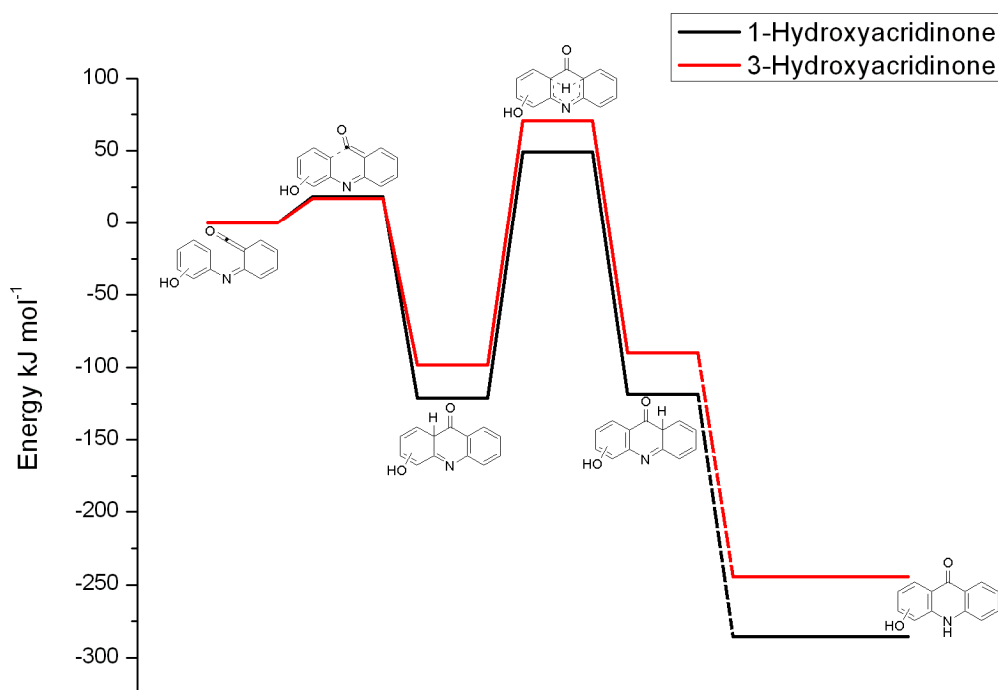


Figure 4.20 Energy surface for the formation of hydroxyacridinones **4.155** and **4.156**

From figure **4.20**, a similar energy profile to that of the hydroxyquinolinones is observed. The 1-hydroxyacridinone is the thermodynamic product in these reactions, with the 1,5-hydrogen shift being the rate determining step in the pyrolysis. The energy surface of 1-hydroxyacridinone against the benzoquinolizone is shown in figure **4.21**.

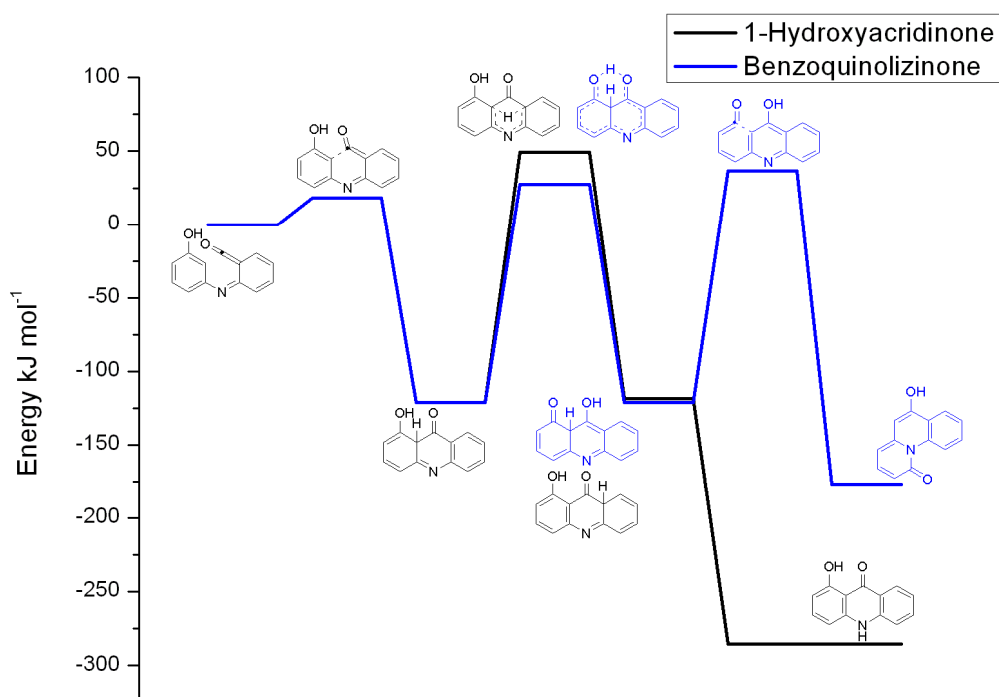


Figure 4.21 Energy surface for the formation of hydroxyacridinone **4.156** and benzoquinolizinone **4.157**

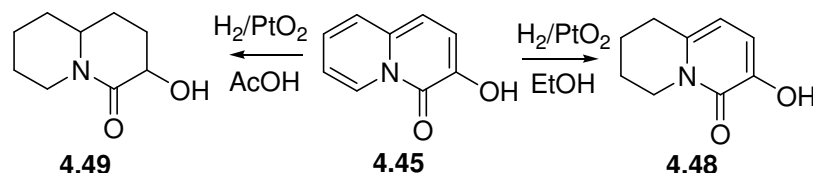
The energy surface for the formation of the hydroxybenzoquinolizinone **4.157** has a number of interesting features. Of note is the hydrogen transfer reaction from the hydroxy group to the carbonyl group, which now has a far higher energy barrier than the corresponding hydroxyquinolizinone surface (27 vs 11 kJ mol⁻¹). The energy to generate quinolinylketene is also larger than the pyridyl ketene (148 vs 88 kJ mol⁻¹). The cyclisation to the benzoquinolizinone is still pseudopericyclic, with no locatable transition state. These two results explain why the reaction does not proceed fully to the benzoquinolizinone as it does in the quinolizinone example.

4.2.7 Reactions of 8-Hydroxyquinolizinones

The reactions of quinolizinones have not been studied in depth in the literature,⁵⁹ but the reactions have targeted two features of the molecule: the π -system, which should be reactive towards electrophilic substitution and hydrogenation reactions, and the amide bond, which for example might be reduced by lithium aluminium hydride to give the 4*H*-quinolizine. With hydroxyquinolizinones, there is also the additional

reaction site of the hydroxy- group.

Hydrogenation of the quinolizinone ring system has been reported before, as well as for hydroxyquinolizinones. An example of this was reported by Jones,⁷³ who found that the regioselectivity of the hydrogenation of 3-hydroxyquinolizinone **4.45** could be controlled by altering the solvent (Scheme **4.85**).



Scheme 4.85 Hydrogenation of 3-hydroxyquinolizinone **4.45**

The electrophilic aromatic substitution reactions of quinolizinones have been reported in a series of papers by Thyagarajan, which included bromination⁸⁹, nitration⁹⁰ and formylation⁹¹ reactions. These papers showed that the parent quinolizinone was highly reactive towards electrophiles, often undergoing a second electrophilic substitution reaction. With an electron-donating hydroxy- group, 8-hydroxyquinolizinone **4.69** should be more reactive towards electrophiles than the parent quinolizinone.

Adams⁷⁴ reported that lithium aluminium hydride did not reduce the amide bond of 6-hydroxyquinolizinone and only insoluble salts were recovered. In this work, attempts to react 8-hydroxyquinolizinone **4.69** with lithium aluminium hydride lead to the formation of an insoluble solid, with no traces of the reduced product.

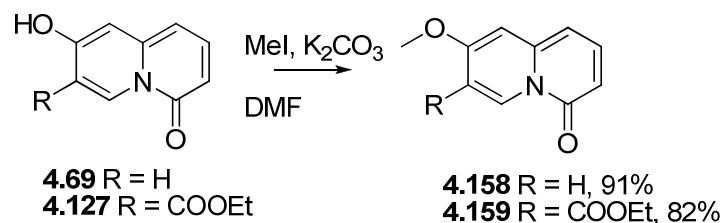
4.2.8 Reactions at 8-Hydroxy Group

The hydroxy- group should be phenolic in nature and therefore should be expected to undergo alkylations, acetylations and other typical reactions of phenols.

4.2.8.1 Alkylation of 8-Hydroxyquinolizinones

Using iodomethane and sodium hydride in DMF, the parent 8-hydroxyquinolizinone

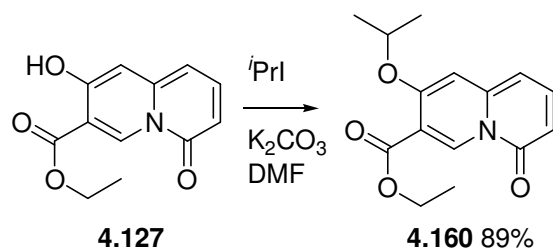
was *O*-methylated in 91% yield. Similarly, the 7-ethyl ester analogue **4.127** could also be *O*-methylated using a milder base, potassium carbonate, under similar conditions,⁹² in a yield of 82% (Scheme 4.86).



Scheme 4.86 Methylation of hydroxyquinolizinones **4.158** and **4.159**

Of interest, is the selectivity of *O*-alkylation over *C*-alkylation under both sets of conditions. Attempts to *O*-allylate or *O*-benzylate compounds **4.69** and **4.127**, using similar conditions gave complex reaction mixtures. Employing Mitsunobu conditions⁹³ (benzyl alcohol, PPh₃, DIAD) also gave similar results.

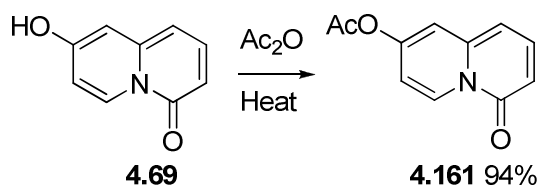
The alkylations are not limited to methylations. Using 2-iodopropane in place of iodomethane, compound **4.160** was synthesised from compound **4.127** in 89% yield. (Scheme 4.87)



Scheme 4.87 Isopropylation of compound **4.127**

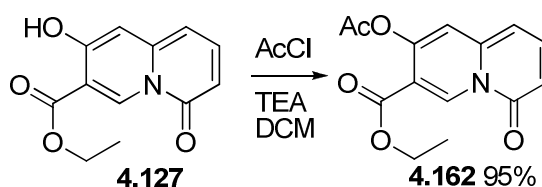
4.2.8.2 Acetylation Reactions of 8-Hydroxyquinolizinone

Acetylation of 8-hydroxyquinolizinone **4.69** was carried out by heating the compound in acetic anhydride for 5 minutes. After removal of the acetic anhydride and purification by distillation, the acetoxy compound **4.161** was obtained in 94% yield (Scheme 4.88).



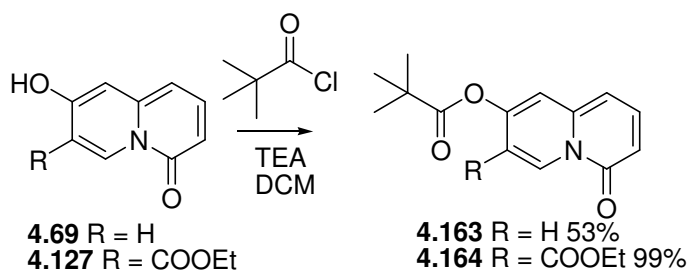
Scheme 4.88 Acetylation of compound **4.69** using acetic anhydride

For the ethyl ester analogue **4.127**, alternative conditions were applied. Using acetyl chloride and triethylamine in DCM at room temperature for 2.5 hours, the acetoxy compound **4.162** was obtained in 95% yield (Scheme 4.89).



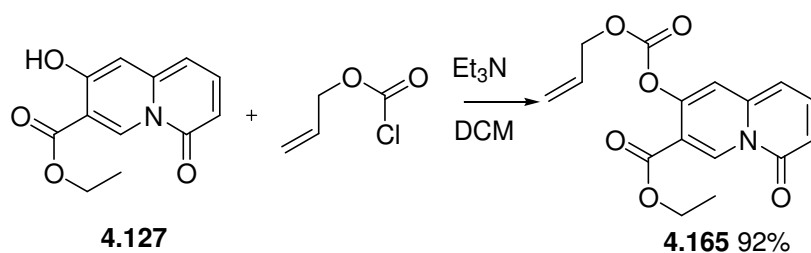
Scheme 4.89 Acetylation of compound **4.127** using acetyl chloride

With both sets of conditions, these acetylation reactions only showed *O*-acetylation with no sign of *C*-acetylation. These conditions were also applied to the synthesis of trimethylacetyl derivatives **4.163** and **4.164** (Scheme 4.90).



Scheme 4.90 Formation of trimethylacetyl compounds **4.69** and **4.127**

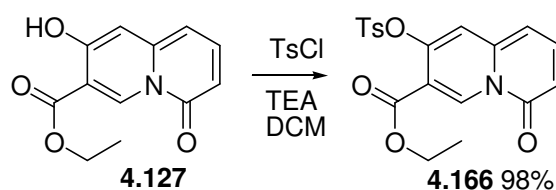
Using similar conditions, it is also possible to form carbonates of 8-hydroxyquinolinizinones. Using allyl chloroformate and triethylamine in DCM, allyloxycarbonyl compound **4.165** was synthesised in 92% yield after work-up (Scheme 4.91)



Scheme 4.91 Synthesis of compound **4.165**

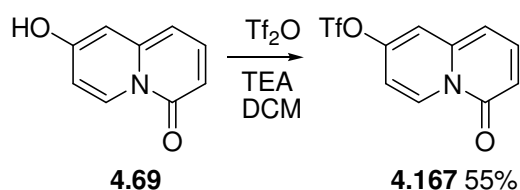
Allyloxycarbonyl compounds have been used to synthesise allyl compounds using a palladium source (typically $\text{Pd}(\text{PPh}_3)_4$).⁹⁴ However attempts to apply these conditions to compound **4.165** gave a complex mixture of products by ^1H NMR spectroscopy.

It was also possible to synthesise *p*-toluenesulfonates of the hydroxyquinolizinones, by using *p*-toluenesulfonyl chloride in place of the acetyl chloride, to give compound **4.166** in 98% yield (Scheme 4.92)



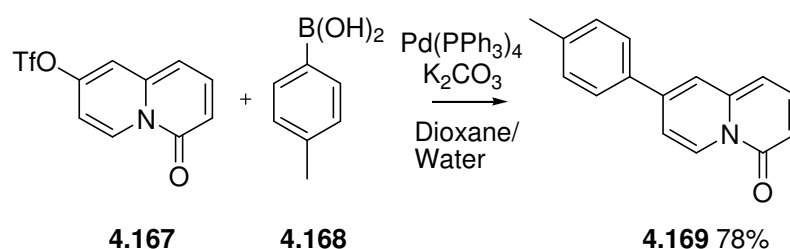
Scheme 4.92 Formation of compound **4.166**

It was possible to convert the hydroxyl group into a trifluoromethylsulfonate group, using trifluoromethane sulfonic anhydride in place of the acetyl chloride (Scheme 4.93). Upon addition of the anhydride, the reaction mixture turns dark and upon work-up, a dark oil is obtained, containing the crude triflate. The product could be used without purification in subsequent reactions, but was found to give depressed yields. Purification of the crude material by column chromatography gave the triflate in moderate yield (48%).



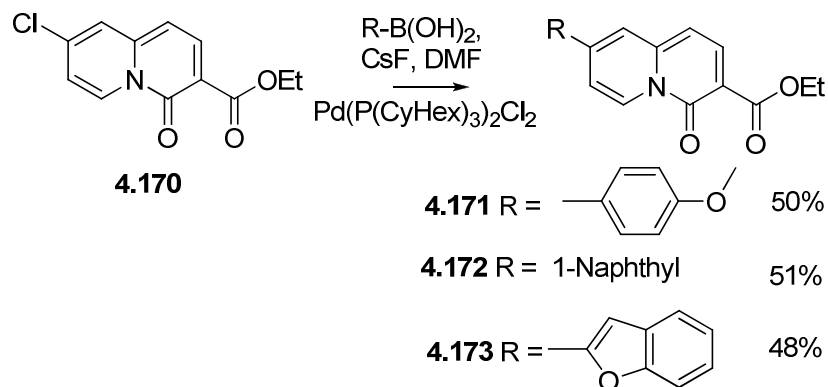
Scheme 4.93 Synthesis of compound **4.167**

Aryl triflates are known to be halide-equivalents in palladium catalysed reactions, such as the Suzuki-Miyaura reaction.⁹⁶ Since compound **4.69** behaves as a phenol, compound **4.167** should behave as an aryl triflate and also participate in these reactions. Using $\text{Pd}(\text{PPh}_3)_4$ as the source of palladium (0),⁹⁵ Suzuki coupling with *p*-tolylboronic acid **4.168** proceeded to give compound **4.169** in 78% yield (Scheme 4.94)



Scheme 4.94 Suzuki coupling of compound **4.167**

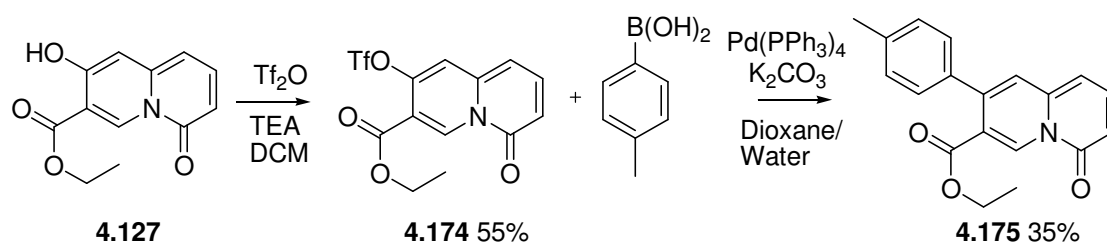
8-Arylquinolizinones have been reported in the literature previously using a similar strategy.⁶¹ Starting from the chloro compound **4.170**, Suzuki cross-coupling gave 8-arylquinolizinones **4.171** – **4.173** (Scheme 4.95)



Scheme 4.95 Suzuki coupling of compound **4.170**

The yields of the three coupled products were around 50%, and in all 3 examples, the quinolizinone is substituted in the 3-position.

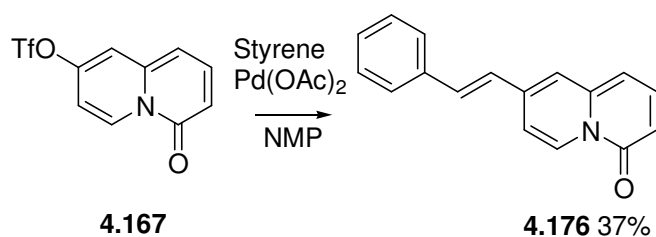
The triflate of ester analogue **4.174** was also synthesised and subjected to the same conditions for the Suzuki coupling (Scheme 4.96)



Scheme 4.96 Synthesis and Suzuki coupling of compound **4.174**

The yield for the triflate formation was similar to that of the parent hydroxyquinolizinone (55%), but the Suzuki coupling proceeded in a lower yield of 35%. Suzuki couplings have been noted for their insensitivity towards *ortho* substituents,⁹⁶ so the lower yields may be representative of the unoptimised conditions used for the coupling reaction.

Another palladium catalysed cross-coupling reaction is the Heck reaction, the reaction of an aryl halide or triflate with an alkene.⁹⁷ Triflate **4.167** was reacted with styrene, using palladium acetate in NMP to give the 8-styryl compound **4.176** in 37% yield (Scheme 4.97).⁹⁸

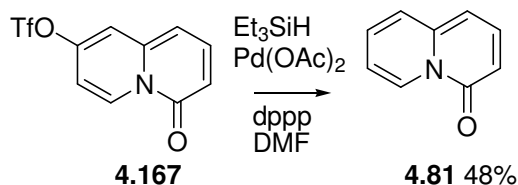


Scheme 4.97 Heck coupling of compound **4.167** with styrene

The low yield for this reaction reflects two points: (i) the low reactivity of styrene in Heck reactions and (ii) the unoptimised conditions used. With further optimisation the yield of the reaction could be improved, but the feasibility of the use of the triflate in Heck-type couplings has been demonstrated.

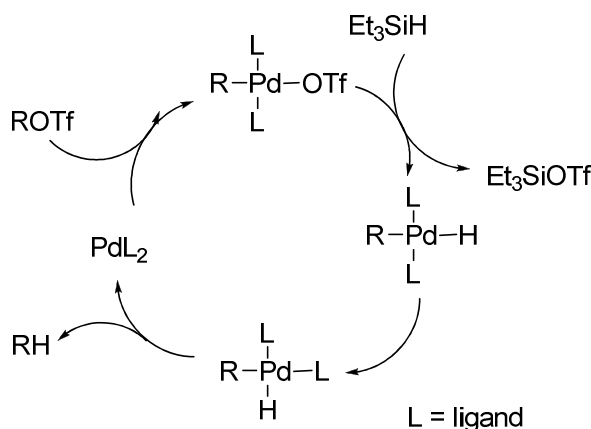
Reduction of triflates by palladium catalysts has also been reported in the literature, using a range of reduction sources, such as tributyltin hydride and tributylammonium formate though metal hydrides (e.g. LiAlH_4) tended to give poor yields.⁹⁹ These

reducing agents have extensively studied for vinyl triflates¹⁰⁰ but not for aryl triflates. A study of the reduction of aryl triflates by triethylsilane has been reported¹⁰¹ and so could be utilised for the potential reduction of compound **4.167** (Scheme **4.98**).



Scheme 4.98 Reduction of compound **4.167** with triethylsilane

Using palladium acetate and 1,3-bis(diphenylphosphino)propane (dppp) as a ligand, the reduction of triflate **4.167** with triethylsilane proceeded in 48% yield. The mechanism for this reaction was not discussed in the original paper, but probably proceeds in a similar fashion to Stille coupling with tributyltin hydride (Scheme **4.99**).



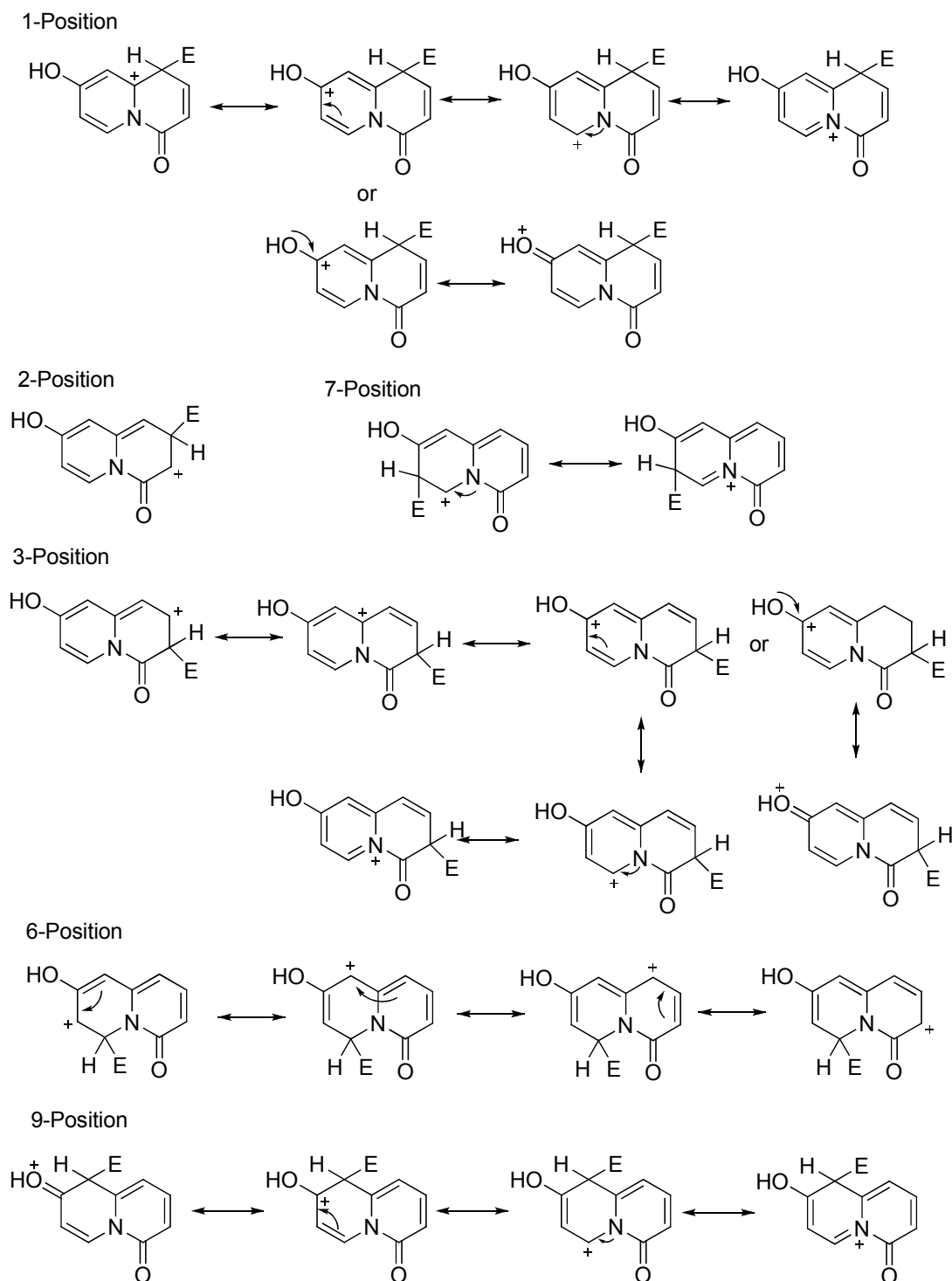
Scheme 4.99 Potential palladium cycle for the reduction of triflates with Et₃SiH

The trans-metallation step now involves the triethylsilane in place of the standard stannane or boronic acid. This involves a hydride transfer to the palladium catalyst, with triethylsilyl triflate as the by-product, hydrolysed on work-up to give triethylsilanol.

The reduction of the triflate compound **4.167** also confirms the structure of 8-hydroxyquinolizinone **4.69**, as the reduction gives the known compound quinolizinone **4.81**, with the ¹H NMR spectrum matching the literature data.⁸⁷

4.2.9 Electrophilic Substitution Reactions of Quinolizinones

Quinolizinones are electron-rich and should be highly reactive towards electrophiles. The regioselectivity of the reactions can be considered from the resonance structures (Scheme 4.100).



Scheme 4.100 Resonance structures for the electrophilic aromatic substitutions of 8-hydroxyquinolizinones

From the number of resonance structures in scheme **4.100**, it can be seen that the two favoured positions for electrophilic substitution reactions should be the 1- and 3- positions of the ring. The next most reactive position is the 9-position, but reaction is unlikely to occur there unless both the 1- and 3- positions are blocked.

For solubility reasons, most reactions were performed on the ester analogue, **4.127**. The improved solubility of compound **4.127** allowed for greater control over regioselectivity by changing both the solvent and the temperature as necessary.

4.2.9.1 Reaction of 8-Hydroxyquinolizinones with Trifluoroacetic Acid

8-Hydroxyquinolizinone was dissolved in [^2H] trifluoroacetic acid and the ^1H NMR spectrum observed over time. The change in the magnitude of an integral shows the percentage incorporation of deuterium into that position. Two protons were observed to change over time, the protons in the 1- and 3- positions as expected. The assignment was based on the chemical shifts in d_6 -DMSO and the amount they change in TFA. This is shown in figure **4.22** (below).

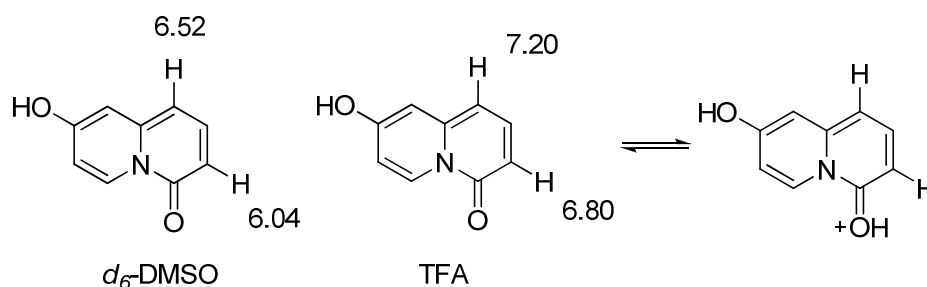
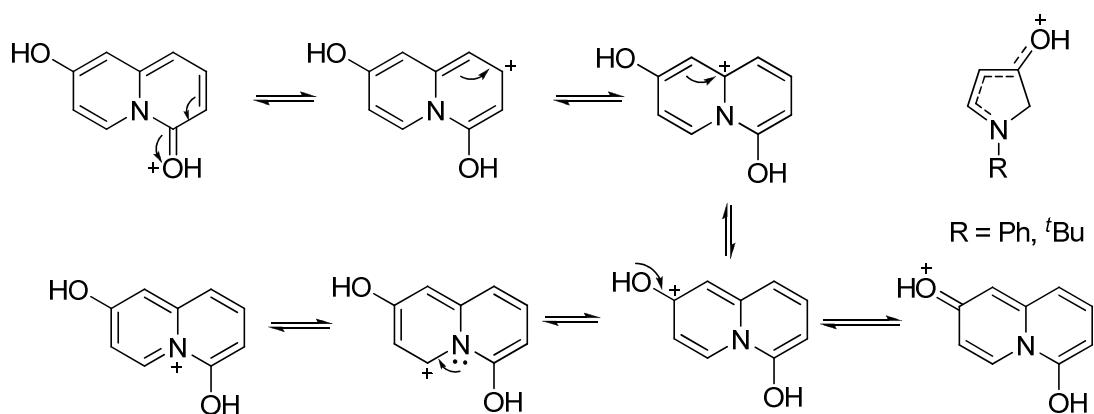


Figure 4.22 ^1H NMR chemical shifts of 8-hydroxyquinolizinone **4.69** in d_6 -DMSO and TFA

In both cases, the chemical shifts of the two protons are roughly 0.7-0.8 ppmn higher in TFA than in DMSO. This is likely to the compound being in equilibrium with its protonated form and delocalisation of the charge across the ring system (Scheme **4.101**). This is comparable with other enaminones, for example *N*-substituted 3-hydroxypyrroles show similar changes in their ^1H NMR spectra in [^2H] trifluoroacetic acid (Scheme **4.101**)



Scheme 4.101 Delocalisation of the charge in 8-hydroxyquinolizinones

In [²H]-TFA, the triplet at $\delta_H = 7.66$ ppm, which must be due to the 2-position, is seen to change slowly over time to a singlet. This shows that it is the 1- and 3- positions that are exchanging. A plot of change of integral over time is shown below (Figure 4.23)

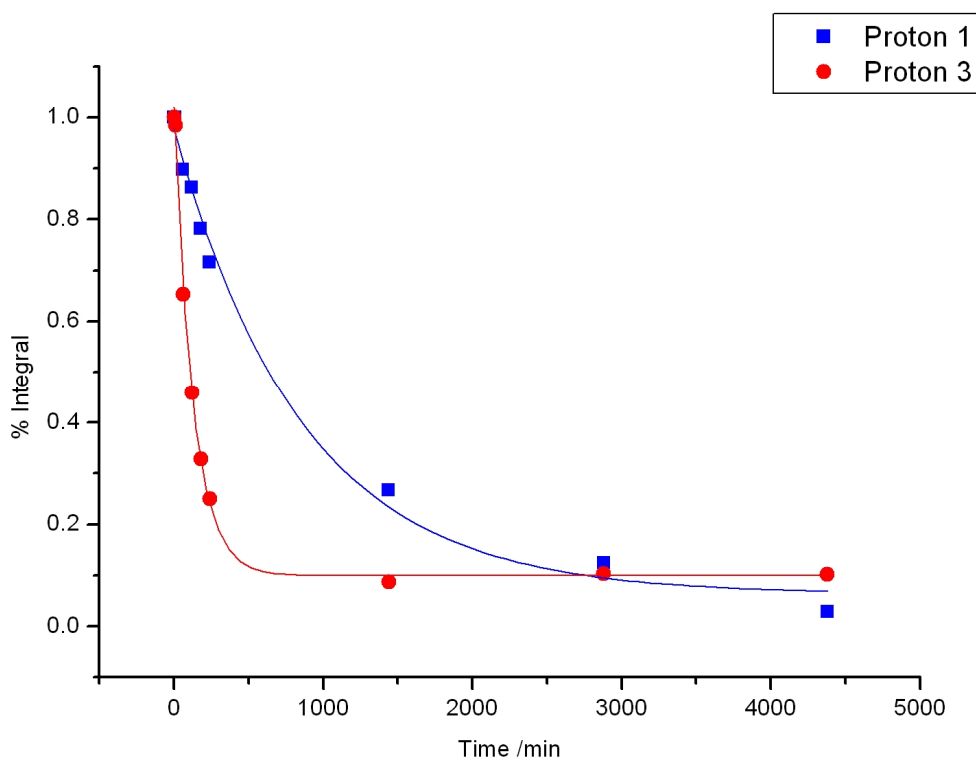


Figure 4.23 Plot of % incorporation of deuterium over time for compound 4.69

It can be seen that the proton in the 3-position exchanges at a faster rate than the 1-position, hinting that other electrophilic substitution reactions may occur there. From this data, rate constants (k) and half-lives can be calculated. This can be done from a plot of \ln of the integral against time, which should give a straight line if the reaction obeys pseudo first order kinetics, with a gradient of k . This plot is shown below (Figure 4.24).

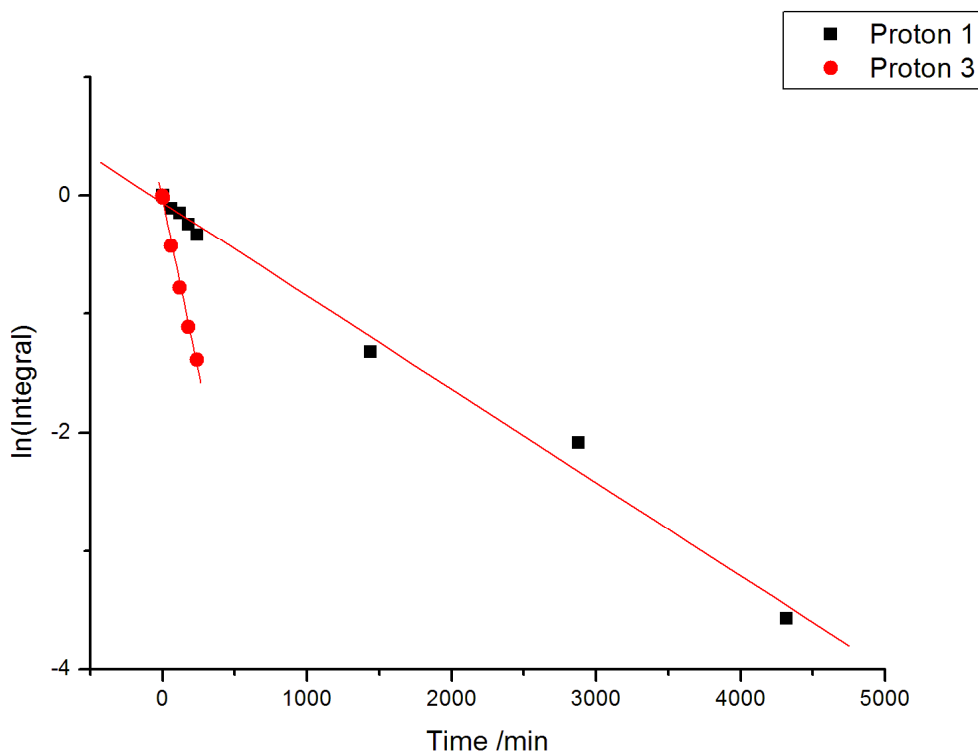


Figure 4.24 Plot of $\ln(\% \text{integral})$ against time for the exchange of compound **4.69** in $[\text{}^2\text{H}]\text{-TFA}$ (Points after equilibration of the exchange were ignored for this plot)

From figure 4.24, two straight lines are observed. For the proton in the 1-position, a pseudo first order rate constant of $7.9 \times 10^{-4} \text{ s}^{-1}$ was calculated from the best fit straight line and for the proton in the 3-position, the rate constant was found to be 0.059 s^{-1} . These values were used to calculate the half lives of the exchange process, which were found to be approximately 15 hours for the proton in the 1-position and 2 hours for the proton in the 3-position.

The ethyl ester analogue **4.127** was also dissolved in $[\text{}^2\text{H}]\text{-TFA}$ and the rate of deuterium exchange observed. The graph showing the percentage intergral change

over time is shown below (Figure 4.25)

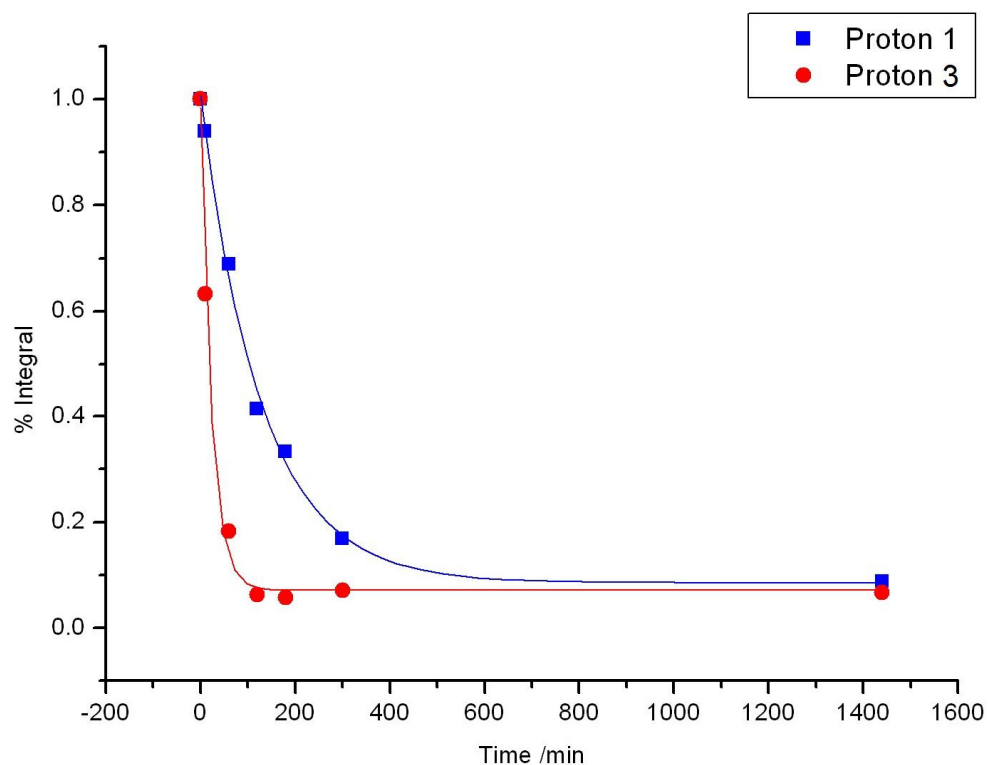


Figure 4.25 Plot of % incorporation of deuterium over time for ester analogue **4.127**

Again, two protons are seen to exchange over time, in the 1- and 3-positions, and proton in the 3-position is seen to exchange at a faster rate. As before, a plot of \ln of the integral against time was obtained and is shown below (Figure 4.26).

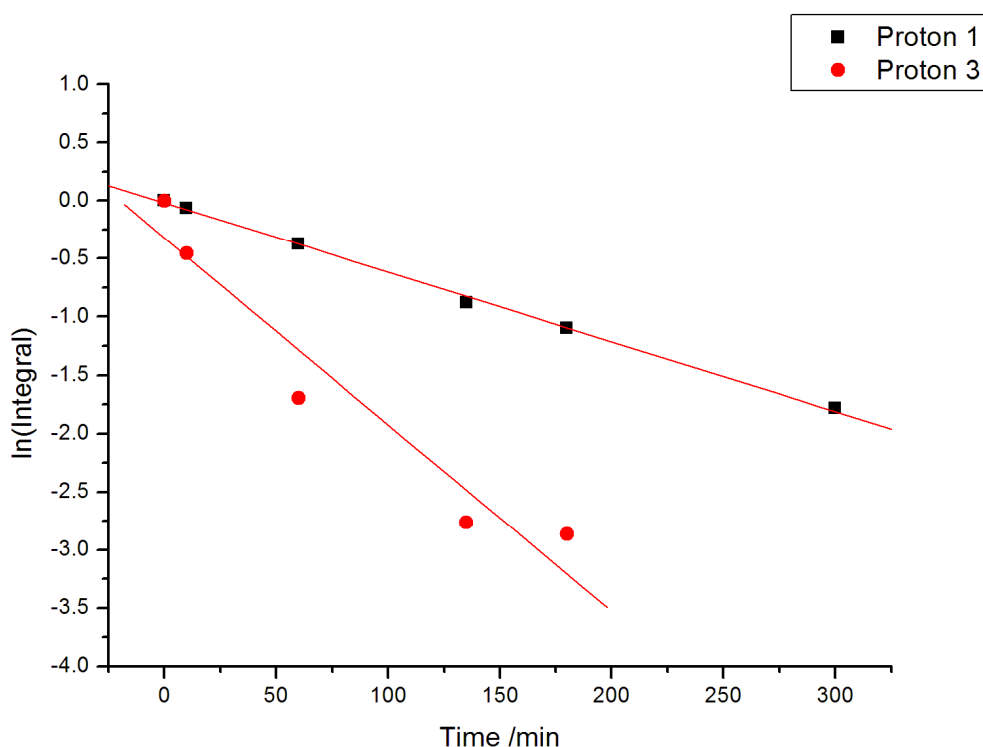
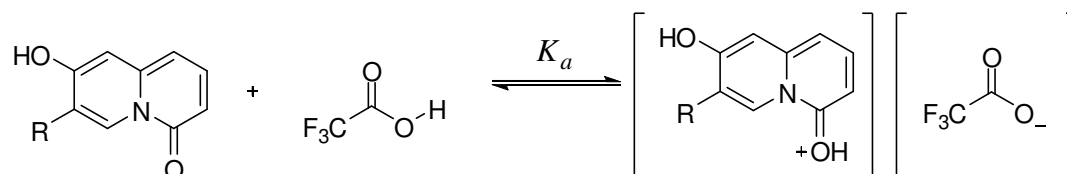


Figure 4.26 Plot of $\ln(\%integral)$ against time for the exchange of compound **4.127** in $[^2H]$ -TFA (Points after equilibration of the exchange were ignored for this plot)

From figure **4.26**, the rate constants were found to be 0.00598 s^{-1} for the proton in the 1-position and 0.0160 s^{-1} for the proton in the 3-position. These values gives half lives of approximately 2 hours for the proton in the 1-position and 45 minutes for the proton in the 3-position.

It is of interest that compound **4.127** undergoes deuterium exchange at a faster rate than compound **4.69**. This initially seems counter-intuitive, as the ester group should make compound **4.127** *less* reactive than compound **4.69** towards electrophilic substitution. However the rate of deuterium exchange is dependent on the concentration of unprotonated species in solution (Scheme **4.102**).



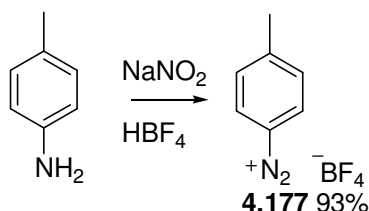
Scheme 4.102 Protonation of hydroxyquinolizinones in TFA

The unprotonated species is most likely the species which undergoes the deuterium exchange. The ester compound most likely has a lower concentration of protonated species in solution, due to the equilibrium lying towards the unprotonated species. With a higher concentration of unprotonated compound, the deuterium exchange would therefore be faster, giving the observed result.

4.2.9.2 Reaction of 8-Hydroxyquinolizinones with Diazonium Salts

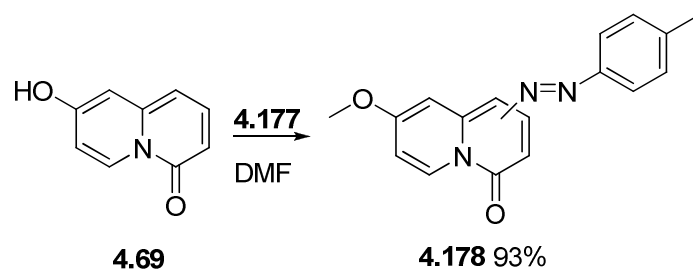
Attempts to couple 8-hydroxyquinolizinone **4.69** or its ethyl ester analogue **4.127** with a diazonium salt generated *in situ* from the corresponding aniline and sodium nitrite gave irreproducible results.

Isolated diazonium salts have also been used for electrophilic aromatic substitution reactions. The *p*-tolyl diazonium tetrafluoroborate salt **4.177** was synthesised according to the literature procedure¹¹⁶ in 93% yield (scheme **4.103**)



Scheme 4.103 Synthesis of *p*-tolyl diazonium tetrafluoroborate **4.177**

Since 8-hydroxyquinolizinone was insoluble in most organic solvents, DMF was chosen as the reaction solvent. To aid work-up, the azo-coupling was followed by addition of potassium carbonate and iodomethane to methylate the coupled product and aid purification of the product. The azo-coupled product **4.178** was isolated in 93% yield after work-up, with trace amounts of a side product believed to be another isomer (scheme **4.104**).



Scheme 4.104 Azo-coupling of 8-hydroxyquinolizinone **4.69**

Attempts to isolate the minor product from the reaction mixture by column chromatography failed. In order to determine the position of the azo-coupling in the major product, a NOESY experiment was performed. The two potential products can be differentiated, based on the presence of NOE between the protons in the 1- and 9-positions, which is only present in the 3-substituted product. The NOESY spectrum for the major product is shown in figure **4.27** (below)

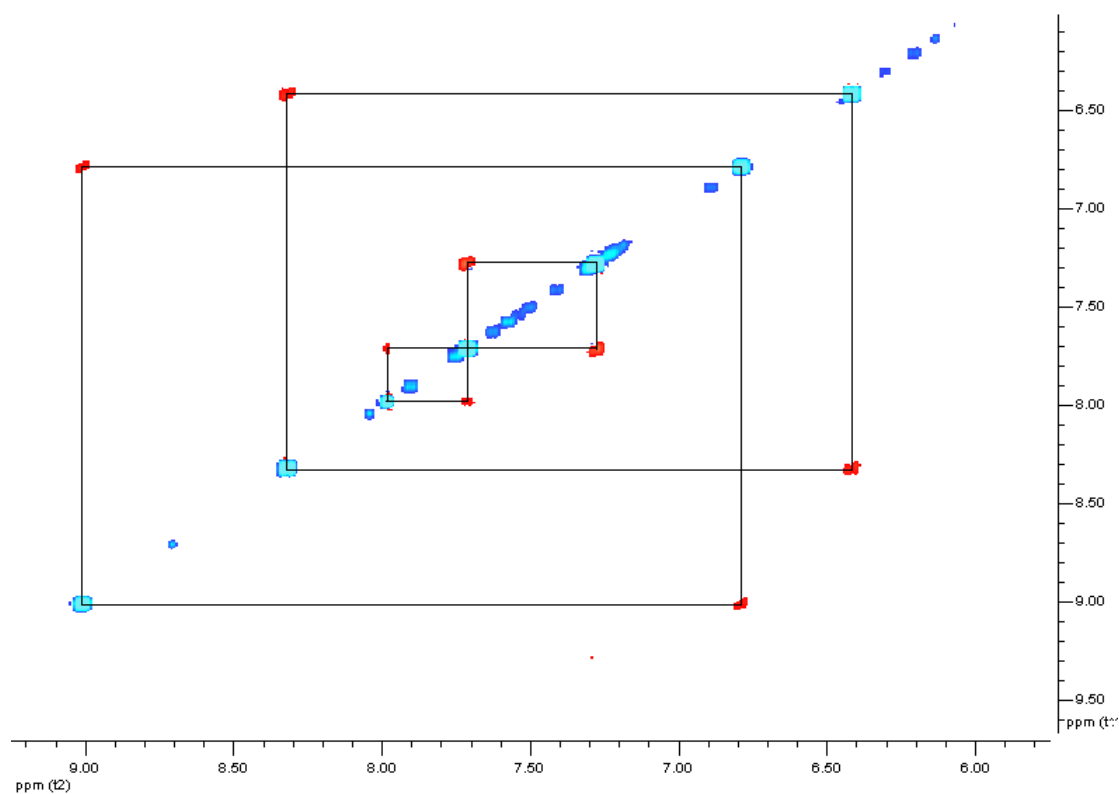


Figure 4.27 NOESY spectrum of compound **4.178**

The small meta-coupled doublet at $\delta_H = 8.0$ ppm, which can only arise from the proton in the 9-position shows two NOE correlations. The first is to the peak at $\delta_H = 4.0$ ppm, the methyl of the methoxy group as expected. The second is to the two proton signal

at $\delta_H = 7.7$ ppm, one of the two signals of the *p*-tolyl ring. The only way this can occur is if the azo-coupling has occurred in the 1-position. The signal from the *p*-tolyl ring at $\delta_H = 7.7$ ppm then shows a NOE signal to the other 2 proton signal at $\delta_H = 7.3$ ppm, assigning that to the other protons in the *p*-tolyl ring. This shows the expected NOE to the 3 proton singlet at $\delta_H = 2.5$ ppm, the methyl group of the *p*-tolyl ring. The peak at $\delta_H = 9.0$ ppm is typical of the 6-position in the quinolizinone ring, shows only 1 NOE, to the proton at $\delta_H = 6.7$ ppm assigning that to the 7-position. The doublet at $\delta_H = 6.4$ ppm is usually due to the proton at either the 1 or 3 positions. Since the 1-position is substituted, this proton is located in the 3-position, and shows an NOE to the proton at $\delta_H = 8.3$ ppm, assigning that to the 2-position. The full assignment of the proton spectra is shown below in table 4.4 and figure 4.28.

Proton	δ_H /ppm	Correlations	Assignment
A	8.98	F	Quinolizinone 6-position
B	8.29	G	Quinolizinone 2-position
C	7.95	H, D	Quinolizinone 9-position
D	7.68	C, E	<i>p</i> -tolyl ring
E	7.25	D, I	<i>p</i> -tolyl ring
F	6.75	A	Quinolizinone 7-position
G	6.38	B	Quinolizinone 3-position
H	3.99	C	8-Methoxy methyl
I	2.41	E	<i>p</i> -Tolyl ring methyl

Table 4.4 NOESY correlations for compound 4.178

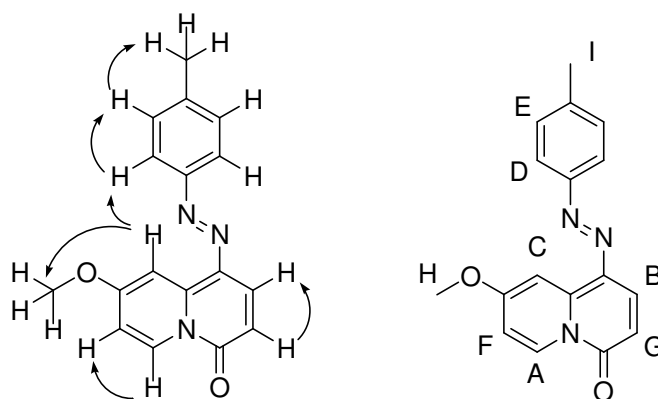


Figure 4.28 NOESY assignments for compound 4.178

To assign the ^{13}C spectrum, a HSQC experiment was performed and is shown below (figure 4.29)

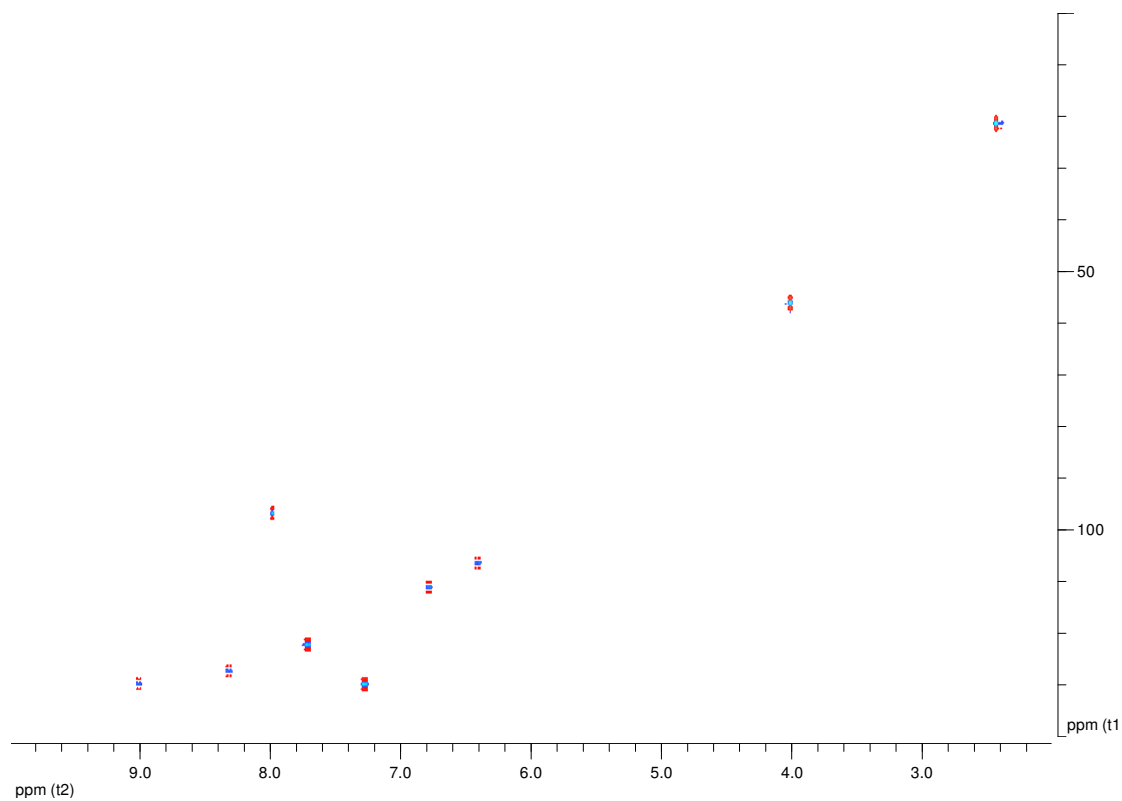


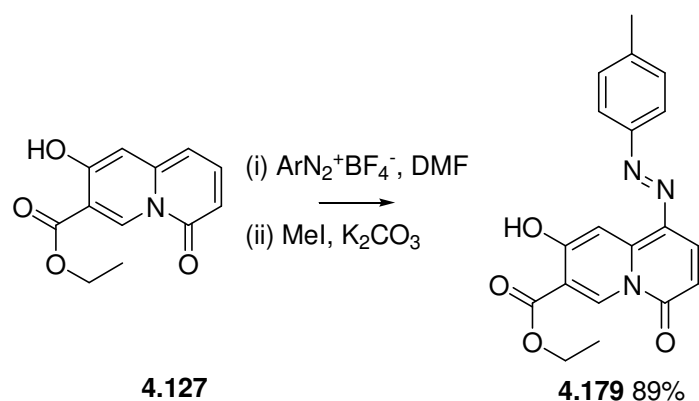
Figure 4.29 HSQC spectrum for compound **4.178**

Since the proton spectrum was assigned from the NOESY experiment, the corresponding carbon atom resonances could be assigned from the HSQC spectrum. These are shown in table 4.5 (below)

δ_H /ppm	δ_C /ppm	Assignment
8.98	129.52	Quinolizine 6-position
8.29	127.03	Quinolizine 2-position
7.95	99.57	Quinolizine 9-position
7.68	121.93	<i>p</i> -tolyl ring
7.25	129.56	<i>p</i> -tolyl ring
6.75	110.84	Quinolizine 7-position
6.38	106.19	Quinolizine 3-position
3.99	56.00	8-Methoxy methyl
2.91	21.32	<i>p</i> -Tolyl ring methyl

Table 4.5 HSQC data for compound **4.178**

The reaction was also performed on the ester analogue **4.127** under the same conditions. This gave an azo-coupled product **4.179** in 89% yield, again with trace amounts of a side product believed to be a minor isomer (Scheme **4.105**).



Scheme 4.105 Azo-coupling for ester analogue **4.127**

The minor product could not be isolated from the reaction mixture by column chromatography, as with 8-hydroxyquinolizine **4.69**. The major isomer could be identified as the 1-azo-coupled product. An X-ray crystal structure of compound **4.179** was also obtained, which clearly shows that the azo-coupling has reacted in the 1-position (Figure **4.30**).

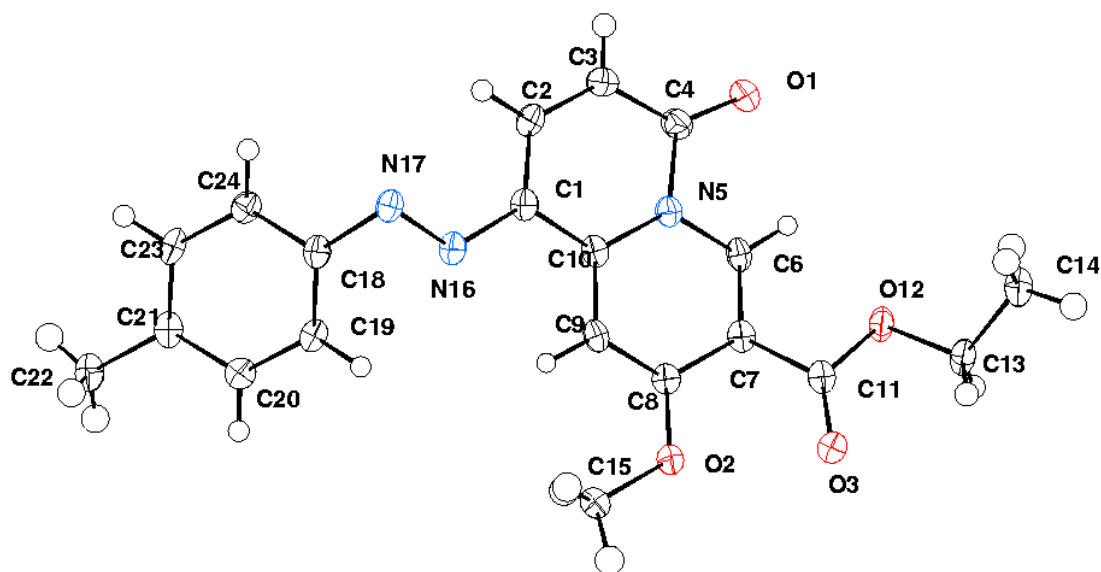


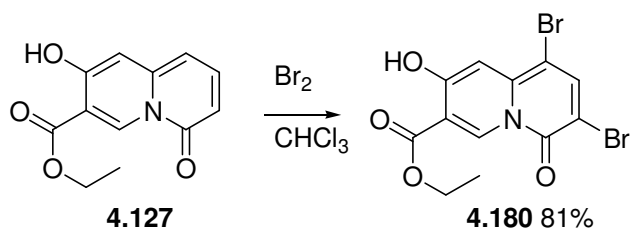
Figure 4.30 Crystal structure of compound **4.179**

The crystal structure shows why the NOE signal between the proton in the 9-position of the quinolizinone and the proton in the *p*-tolyl ring is observed in **4.179**, due to their close proximity in space.

4.2.9.3 Halogenation of 8-Hydroxyquinolizinones

Quinolizinone itself has been shown to undergo bromination reactions readily.⁸⁷ The use of bromine in acetic acid gives the 1,3-dibrominated product in 70% yield. Monobromination was achieved by the use of ethyl bromide in DMSO, to give 3-bromoquinolizinone in 39% yield. The mechanism for this unusual reaction was not reported and no references were given for the use of these conditions in bromination reactions.

Addition of bromine to a solution of compound **4.127** in chloroform lead to the formation of a thick precipitate of the dibrominated product **4.180**. Concentration of the filtrate also gave the dibrominated product, isolated in a combined yield of 81% (Scheme **4.106**).



Scheme 4.106 Dibromination of compound **4.127**

Addition of 1 equivalent of *N*-bromosuccinimide to a solution of compound **4.127** in DCM gave a mixture of four different products. Two of them could be identified as the dibrominated product **4.180** and starting material. Based on the remaining signals, the other two products were the two likely mono-brominated regioisomers. In order to assign the identity of the two products, the mixture was *O*-methylated and an attempt was made to isolate the products by column chromatography. However only one of the regioisomers could be isolated in a small quantity, with the other regioisomer contained in the mixed fractions. The quantity was sufficient to characterise the pure compound. A NOESY experiment was performed, in order to establish the position of the bromine (Figure 4.31)

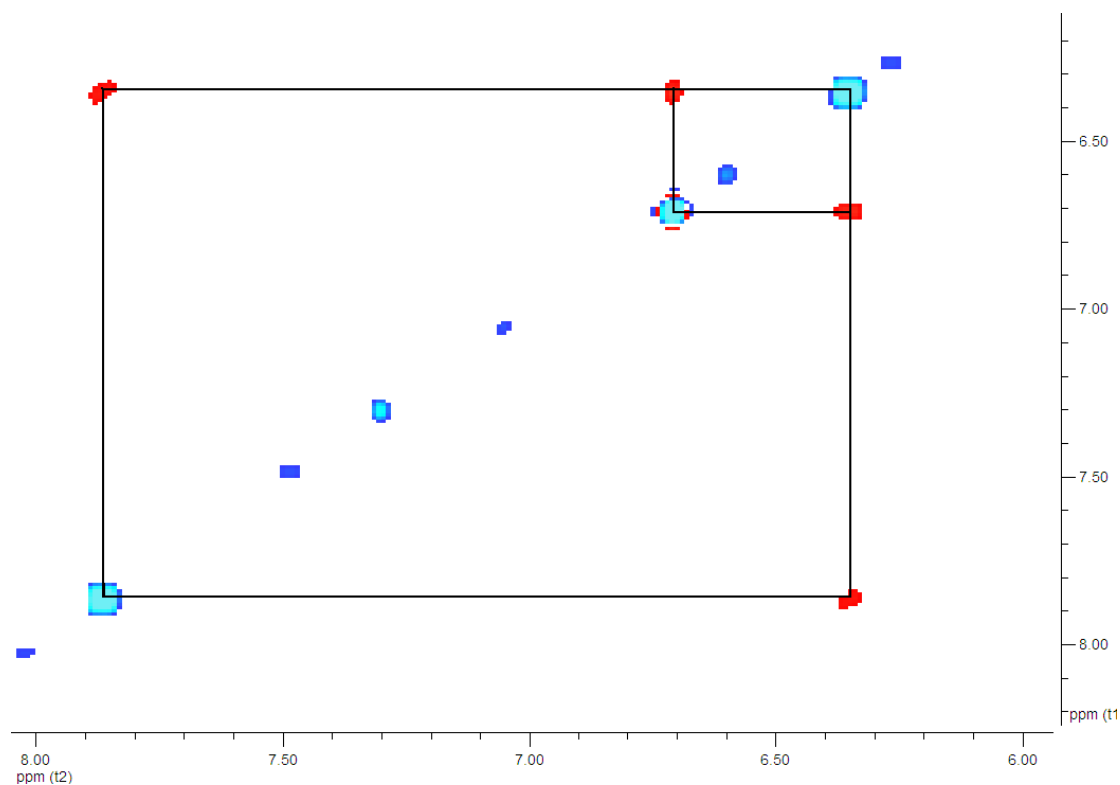


Figure 4.31 NOESY spectrum of the major monobrominated product

The correlation of the methoxy peak of the *O*-methylated monobromo compound at $\delta_H = 3.8$ ppm, to the singlet at $\delta_H = 6.8$ ppm identifies the singlet as due to the 9-position. The other singlet at $\delta_H = 9.5$ ppm is typical of the 6-position in the quinolizinone ring. The proton in the 9-position shows a correlation to the proton at $\delta_H = 6.4$ ppm. The correlation can only occur if the 1-position is unsubstituted. The correlation of the peak at $\delta_H = 6.4$ ppm to the singlet at $\delta_H = 7.8$ ppm assigns the proton at $\delta_H = 7.8$ ppm to the 2-position. This proton shows no further correlations, indicating that the 3-position is substituted. Therefore the isolated product is the 3-brominated product (Figure 4.32)

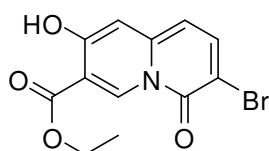


Figure 4.32 Structure of compound **4.181**

Having assigned the four possible products from the bromination, the focus was now on maximising the regioselectivity to obtain a single regioisomer. Various different conditions were attempted and are described below (Table 4.6)

Entry	Conditions	%3-Br	%1-Br	%DiBr	%SM
1	NBS, CH ₂ Cl ₂ , rt, 30 min	22	13	20	45
2	NBS, THF, rt, 30 min*	11	11	64	14
3	NBS, HFIP, rt, 30 min	38	23	17	22
4	NBS, MeCN, rt, 30 min	45	9	23	23
5	DBDMH, CH ₂ Cl ₂ , rt, 30 min	33	19	19	29
6	NBS, CF ₃ SO ₃ H, CHCl ₃ , -20 C to rt	20	0	27	53
7	NBS, CH ₂ Cl ₂ , -78 C to rt, 15 min	76	10	4	10
8	DBDMH, CH ₂ Cl ₂ , -78 C to rt, 15 min	84	11	2.5	2.5

*Contains other complex products

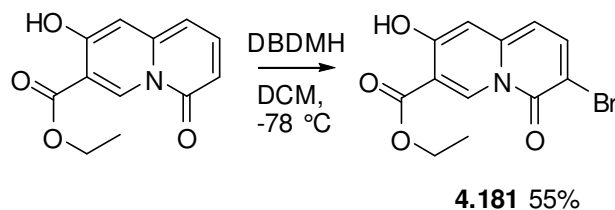
Table 4.6 Alternative bromination conditions, 1.05 equivalents of brominating agent was used in each reaction

Entries 1-4 represent the effect the change of solvent on the bromination ratio. In general the amount of the dibrominated product stayed constant, except in THF. The reaction in THF showed a large amount of other impurities in the ^1H NMR spectrum, complicating the spectrum. Hexafluoroisopropanol (HFIP) has been reported to stabilise intermediates in reactions involving cationic species,¹⁰² so could benefit electrophilic aromatic substitution reactions. Both HFIP and acetonitrile both slightly improved the regioselectivity of the bromination, but not enough to be of use as a preparative method of one of the monobrominated compounds.

Entry 5 represents the use of an alternative source of bromine, 1,3-dibromo-5,5-dimethylhydantion (DBDMH). The ratios are similar to that of *N*-bromosuccinimide, but with more of the 3-brominated product compared to starting material.

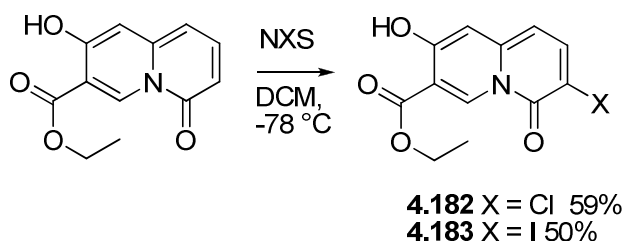
Entry 6 replicates the conditions reported by Oberhauser.¹⁰³ The use of trifluorosulfonic acid and NBS has been reported to aid electrophilic aromatic substitution reactions of phenols. In this example, a large amount of starting material was present, along with 3-brominated and dibrominated products. None of the 1-brominated product was observed.

Entries 7 and 8 represent the effect of temperature on the bromination. If the rate of bromination is fast at room temperature, leading to poor regioselectivity and dibromination reactions, then cooling the reaction should slow the rate of reaction and give better regioselectivity. From the results, the amount of 3-brominated product was greatly increased with small amounts of the other products. DBDMH was found to give improved regioselectivity over NBS, with less of the dibrominated product and starting material. Using these conditions, the 3-brominated product **4.181** could be isolated by recrystallisation of the crude material from isopropyl alcohol (Scheme **4.107**).



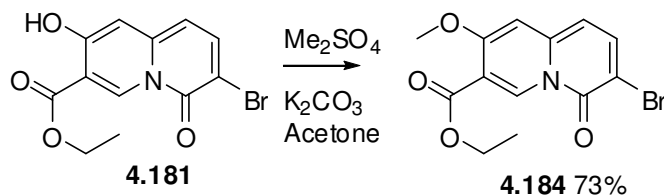
Scheme 4.107 Monobromination of compound **4.181**

These conditions were also applied to chlorination and iodination using the appropriate *N*-halogenosuccinimides to give 3-halogeno products **4.182** and **4.183** in fair yields after recrystallisation (Scheme **4.108**).



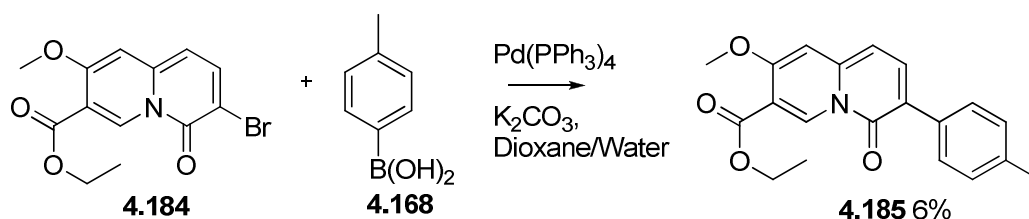
Scheme 4.108 Halogenation of compound **4.127**

Using the 3-bromo compound **4.181**, Suzuki cross couplings were attempted. However the reaction returned a complex mixture, believed to be due to the free hydroxyl causing unwanted side reactions. To counter this, the 3-bromo compound was methylated using dimethyl sulfate, potassium carbonate in refluxing acetone, giving the methylated product in 73% yield (Scheme **4.109**).



Scheme 4.109 Methylation of compound **4.181**

This compound was then subjected to Suzuki coupling, using similar conditions⁹³ to that used previously (Pd(PPh₃)₄, K₂CO₃, Dioxane/Water) with *p*-tolylboronic acid **4.168** to give the 3-*p*-tolyl product **4.185** in 6% yield after column chromatography (Scheme **4.110**).



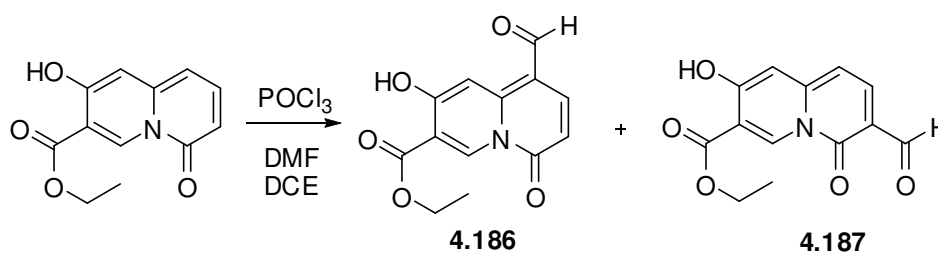
Scheme 4.110 Sukuki coupling of compound **4.184** with *p*-tolylboronic acid **4.168**

The poor yield for the reaction reflects the unoptimised conditions used. With further optimisation, this might be improved but was beyond the scope of the present work.

4.2.9.4 Formylation of 8-Hydroxyquinolizinones

Formylation of quinolizinone under Vilsmeier conditions⁹⁰ (DMF/ POCl_3) has been reported to give the 1-formyl product as the major isomer, with 3-formylated product formed as a minor product. With excess POCl_3 , 1,3 diformylquinolizinone was obtained.

Formation of the Vilsmeier reagent by addition of POCl_3 to DMF, then addition of compound **4.127** in dichloroethane gave two products in a 70:30 ratio, with an overall yield of 93%.¹⁰⁴ Recrystallisation of the crude mixture from ethyl acetate gave the major product in 43% yield. The other isomer was obtained in 9% yield by column chromatography. Both products had molecular ions with $m/z = 261$, indicating that both were mono-formylated products. The two expected products are therefore the 1-formyl compound **4.186** and 3-formyl compound **4.187**, based on the reactivity of quinolizinones towards electrophiles (Scheme **4.111**).



Crude material: 94%, 70:30 mix of two isomers

Scheme 4.111 Formylation of compound **4.127**

The ^1H NMR spectrum of the major component showed the presence of an aldehyde peak at $\delta_H = 9.84$ ppm, supported by a signal in the ^{13}C NMR spectrum at $\delta_C = 188.29$ ppm. In order to assign the position of the aldehyde group, a NOESY experiment was performed and the spectrum obtained is shown below (Figure 4.33)

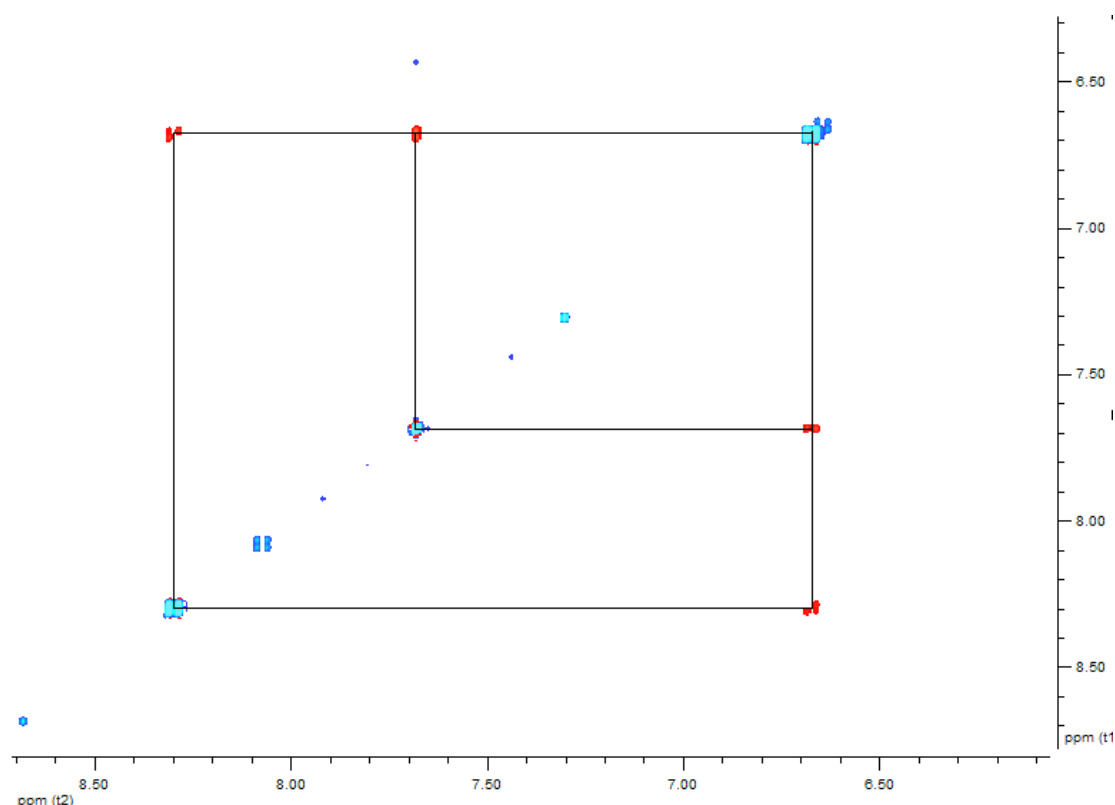


Figure 4.33 NOESY spectrum of the major formylated product

The NOESY shows the doublet at $\delta_H = 6.6$ ppm gives rise to two correlations, one to the doublet at $\delta_H = 8.3$ ppm and the other to the singlet at $\delta_H = 7.8$ ppm. The only way this pattern of correlations can occur is for the doublet at $\delta_H = 6.6$ ppm to be the proton in the 1-position of the ring, the doublet at $\delta_H = 8.3$ ppm to be that at the 2-position and the singlet at $\delta_H = 7.8$ ppm to be that in the 9-position. From this, it can be deduced that the formyl group is in the 3-position of the molecule (Figure 4.34).

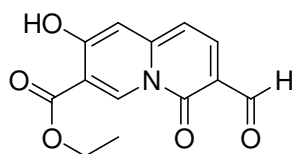


Figure 4.34 Structure of 3-formyl compound **4.187**

The minor component showed the presence of a single aldehyde as expected at $\delta_H = 9.86$ ppm, $\delta_C = 187.34$ ppm, as expected from a mono formylated product. The NOESY spectrum of the compound is shown below (Figure 4.35)

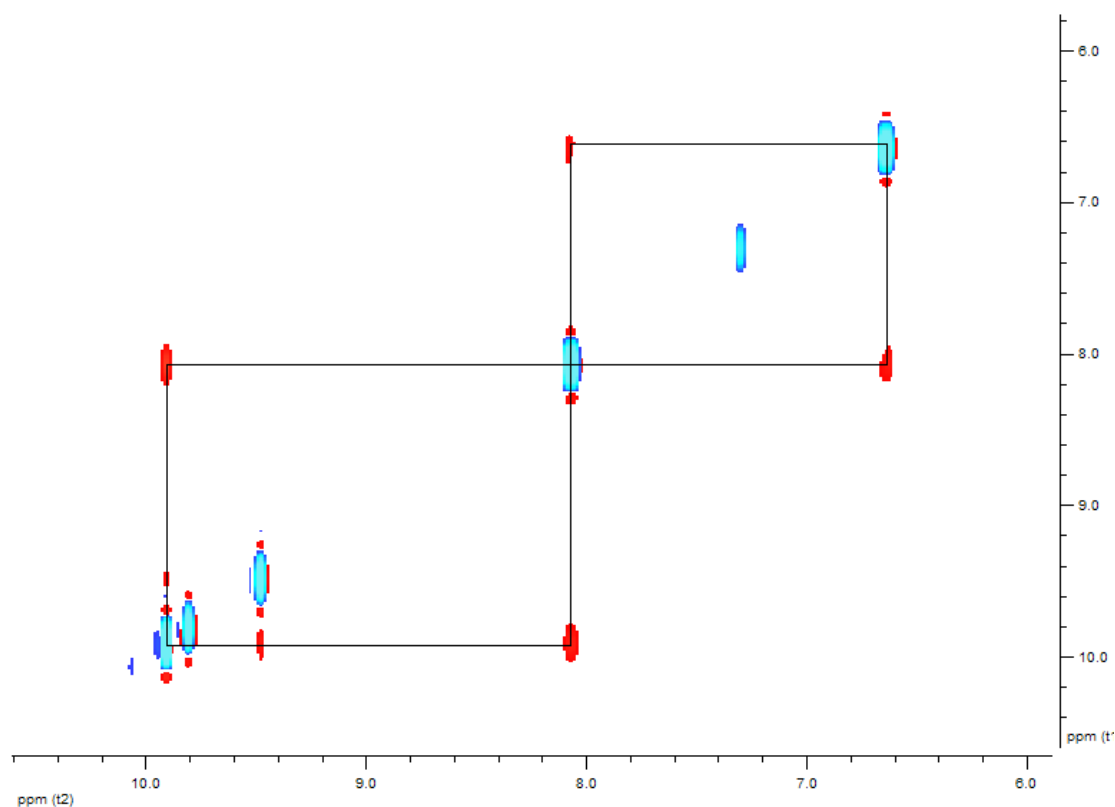


Figure 4.35 NOESY spectrum of minor formylated product

The NOESY of the minor product shows the doublet at $\delta_H = 6.6$ ppm shows a correlation to the doublet at $\delta_H = 8.0$ ppm. This doublet in turn shows a correlation to the singlet at $\delta_H = 9.9$ ppm, which in turn shows a correlation to a singlet at $\delta_H = 9.4$ ppm. Since the major product was identified as the 3-formylated product, the minor product would be assumed to be the 1-formylated product **4.186**. The NOESY data fits with this, as the proton at $\delta_H = 9.9$ ppm would be the aldehyde proton, correlating with the proton in the 9-position in the quinolizinone ring (Figure 4.36).

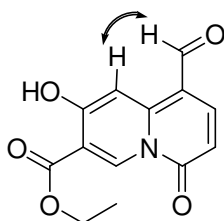
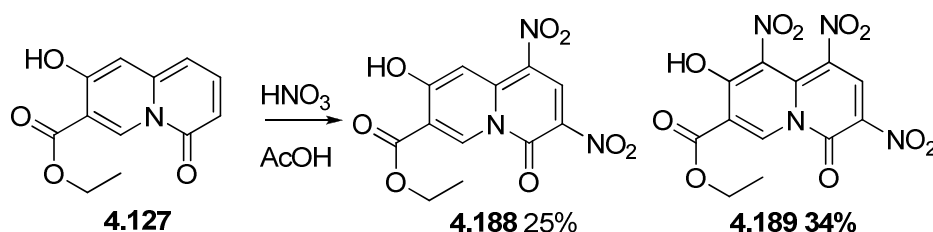


Figure 4.36 Structure of 1-formyl compound **4.186**

Nitration of 8-Hydroxyquinolizinones

Nitration of the parent quinolizinone with concentrated nitric acid at 0 °C gives 1,3-dinitroquinolizinone.⁸⁹ The use of cupric nitrate in acetic anhydride gives a mixture of the 1- and 3-mononitrated products, along with the dinitro product. It was reportedly difficult to isolate these products, without further nitration occurring.

Addition of concentrated nitric acid to a solution of quinolizinone **4.127** in acetic acid gave a brown solid and separation of the two products by column chromatography gave the two compounds in isolated yields of 25% and 35%. From the NMR spectrum of the crude material, these could be identified as the dinitro compound **4.188** and trinitro compound **4.189** respectively (Scheme 4.112).



Scheme 4.112 Nitration of compound **4.127**

The minor product showed the presence of three singlets in the ^1H NMR spectrum at $\delta_{\text{H}} = 7.5$, 9.2 and 9.3 ppm, consistent with the dinitro compound **4.188**. The major product showed a ^1H NMR spectrum with only two singlets in the aromatic regions at $\delta_{\text{H}} = 9.7$ and 9.1 ppm. The negative-ion electrospray mass spectrum of the compound showed m/z of 367, consistent with a molecular ion at m/z $[(\text{M}-\text{H})^-]$ of 368. This mass would correspond to a trinitro species. In terms of reactivity, the next most reactive position after the 1- and 3- positions is the 9-position, so the major product is likely to

be the 1,3,9-trinitro compound **4.189**.

4.2.9.6 Overview of Electrophilic Aromatic Substitution Reactions of 8-Hydroxyquinolizinones

The above work has shown that 8-hydroxyquinolizinones are highly reactive towards electrophiles, in some cases undergoing multiple substitutions. The reactions of both 8-hydroxyquinolizinone **4.69** and its ethyl ester analogue **4.127** are summarised in table **4.7** (below)

Electrophile	Compound 4.69	Compound 4.127
D ⁺	N/A	N/A
ArN ₂ ⁺	90:10	90:10
POCl ₃ /DMF	N/A	30:70
Br ⁺ *	N/A	12:88
NO ₂ ⁺	N/A	N/A

*Using optimised conditions

Table 4.7 Electrophilic aromatic substitution reactions of compounds **4.69** and **4.127** (Ratios are quoted %1-isomer:%3-isomer, nitration is quoted as a ratio of di-substituted to tri-substituted products)

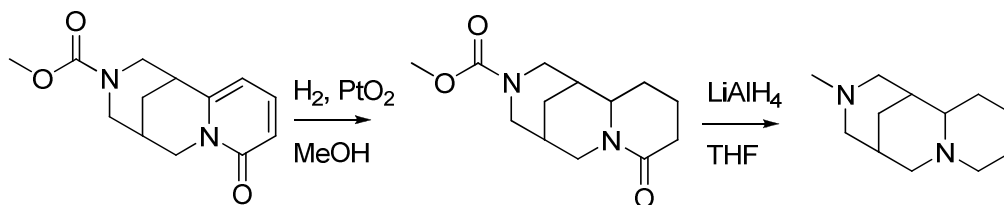
Overall there is no relationship between the electrophile and the regioselectivity of the substitution reaction. While the deuterium exchange reaction suggests that mild electrophiles react in the 3-position first, followed by the 1-position, reaction with diazonium salts (a weak electrophiles) gives the 1-substituted product as the major product. More reactive electrophiles, such bromination and nitration, tend to undergo multiple substitutions.

4.2.10 Hydrogenation of 8-Hydroxyquinolizinones

Hydrogenation of quinolizinones has been reported several times in the literature.⁷³ Generally it requires two different solvents: the first, typically acetic acid, to hydrogenate the “left hand” ring and the second, ethanol, to hydrogenate the pyridone ring. The catalyst utilised to perform this is usually platinum oxide, though Raney nickel in conjunction with high pressure has also been utilised.¹⁰⁵

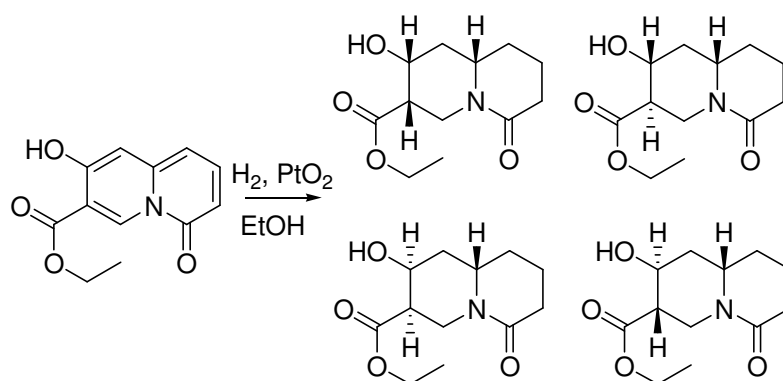
Attempts to hydrogenate 8-hydroxyquinolizinone **4.69**, 8-hydroxy-6-methylquinolizinone **4.118** or ethyl 8-hydroxyquinolizinone-7-carboxylate **4.127**, under high pressure with various solvents and catalysts, lead to irreproducible results. The amounts of hydrogenation varied, even with the same conditions, and often samples contained paramagnetic impurities, which could not be removed even by filtration through celite or silica plugs.

A recent report on the synthesis of (+)-sparteine surrogate involves the hydrogenation of a quinolizinone-like system, using platinum oxide and methanol at room temperature and one atmosphere of hydrogen (scheme **4.113**).¹⁰⁶



Scheme 4.113 Synthesis of a (+)-sparteine surrogate

Application of these conditions to the hydrogenation of ethyl 8-hydroxyquinolizinone-7-carboxylate **4.127** led to the formation of a clear oil. The ¹H NMR spectrum showed the hydrogenation to have gone to completion, as a mixture of three of the four possible diastereomers in the ratio 73:13:13 (Scheme **4.114**).



Scheme 4.114 Hydrogenation of compound **4.127**

Using platinum oxide as the catalyst, a clean sample of the major diastereomer **4.190** was obtained in a 20% yield by column chromatography. The ^1H NMR spectrum of the product is shown below (Figure 4.37)

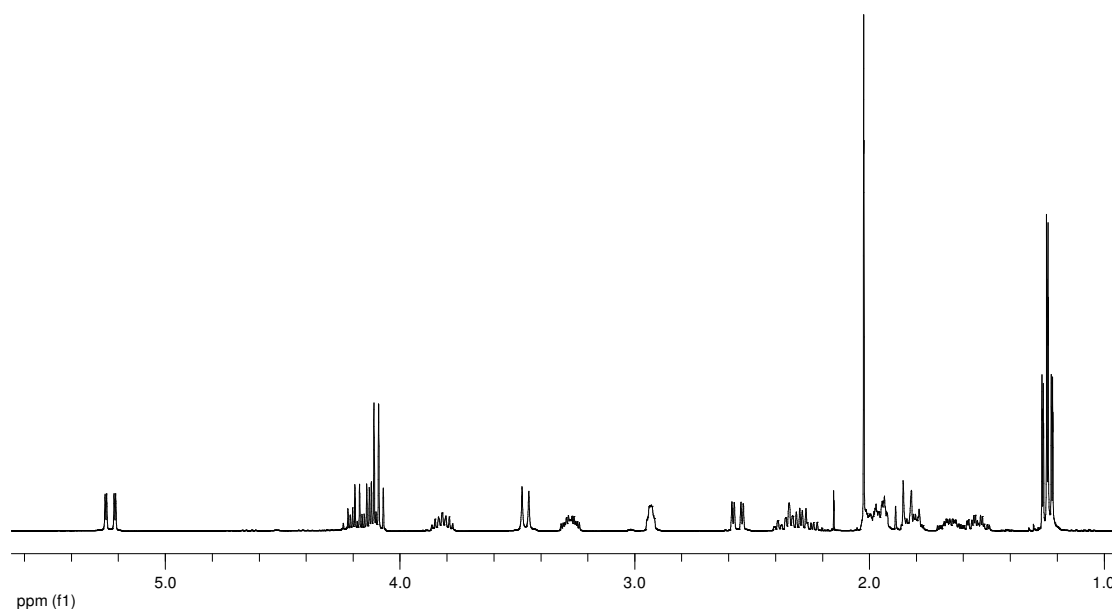


Figure 4.37 ^1H NMR spectrum of compound **4.190**

In figure 4.37, a doublet is observed at $\delta_H = 5.2$ ppm, a high chemical shift for any aliphatic proton. This proton is due to the proton in the equatorial position of C6 in the molecule, which is in the deshielding zone of the carbonyl similarly to that in 8-hydroxyquinolizinone (Figure 4.38)

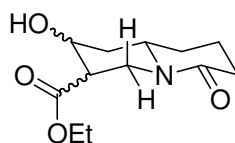


Figure 4.38 Deshielding of the equatorial position of C6 due to the carbonyl at C4

A COSY experimental may aid in assigning more of the protons in the spectrum (Figure 4.39)

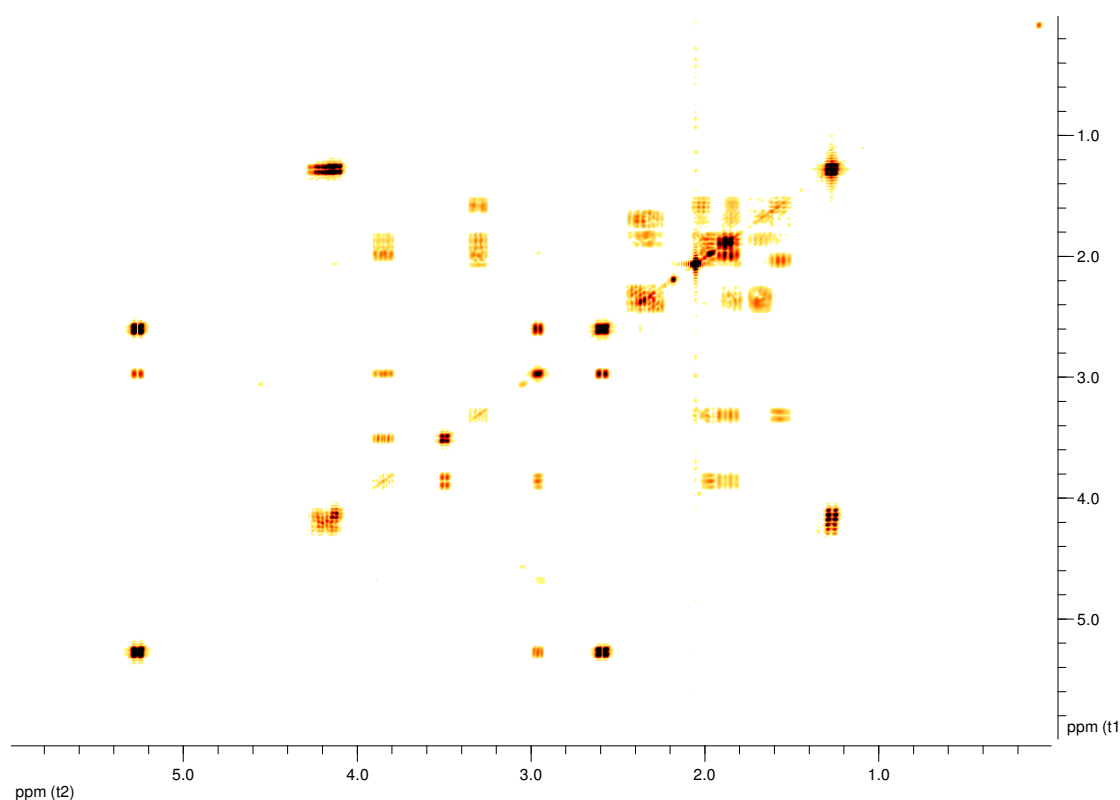


Figure 4.39 COSY spectrum of compound 4.190

The COSY spectrum shows that the peak at $\delta_H = 5.2$ ppm correlates to two further protons, one at $\delta_H = 2.8$ ppm with a weak interaction and more intense one at $\delta_H = 2.6$ ppm. The more intense proton shows a large coupling constant of 13.9 Hz, similar to that of the proton at $\delta_H = 5.2$ ppm. This is indicative of a geminal coupling, assigning the proton to the axial position of C6. This assigns the other proton to C7, but with unknown stereochemistry (Figure 4.40).

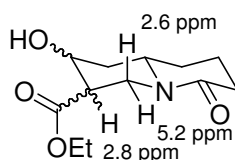


Figure 4.40 Chemical shifts of C6 and C7 of the major diastereomer **4.190**

Both the protons at C6 show small coupling constants of 2-3 Hz along with the large geminal coupling. If the ester at C7 is equatorial, therefore placing the proton axial, we would expect a large coupling for the axial proton at C6. This is not observed, so the proton at C7 must be equatorial. The C7 proton shows another COSY signal to the proton at $\delta_H = 3.8$ ppm, which assigns that proton to the C8 position. The proton at C8 shows three COSY signals, one to the doublet at $\delta_H = 3.6$ ppm and a further two to the multiplet at $\delta_H = 2.0$ ppm. The doublet at $\delta_H = 3.6$ ppm can only arise from the hydroxyl hydrogen and was confirmed by a HQSC experiment (Figure 4.41).

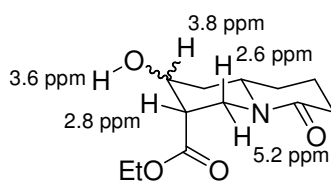


Figure 4.41 Assignment of the major diastereomer **4.190** from the COSY data

This assigns the other two protons at the multiplet at $\delta_H = 2.0$ to the 9 position of the molecule. These two protons both show a COSY signal to the proton at $\delta_H = 3.2$ ppm, which assigns that proton to the ring junction carbon. The remaining protons are contained within the multiplets at $\delta_H = 2.0 - 1.2$ ppm.

In order to assign the stereochemistry of protons at C8 and the ring junction, ROE experiments were performed. First irradiating the proton at C8 positions, the following spectrum was obtained (Figure 4.42)

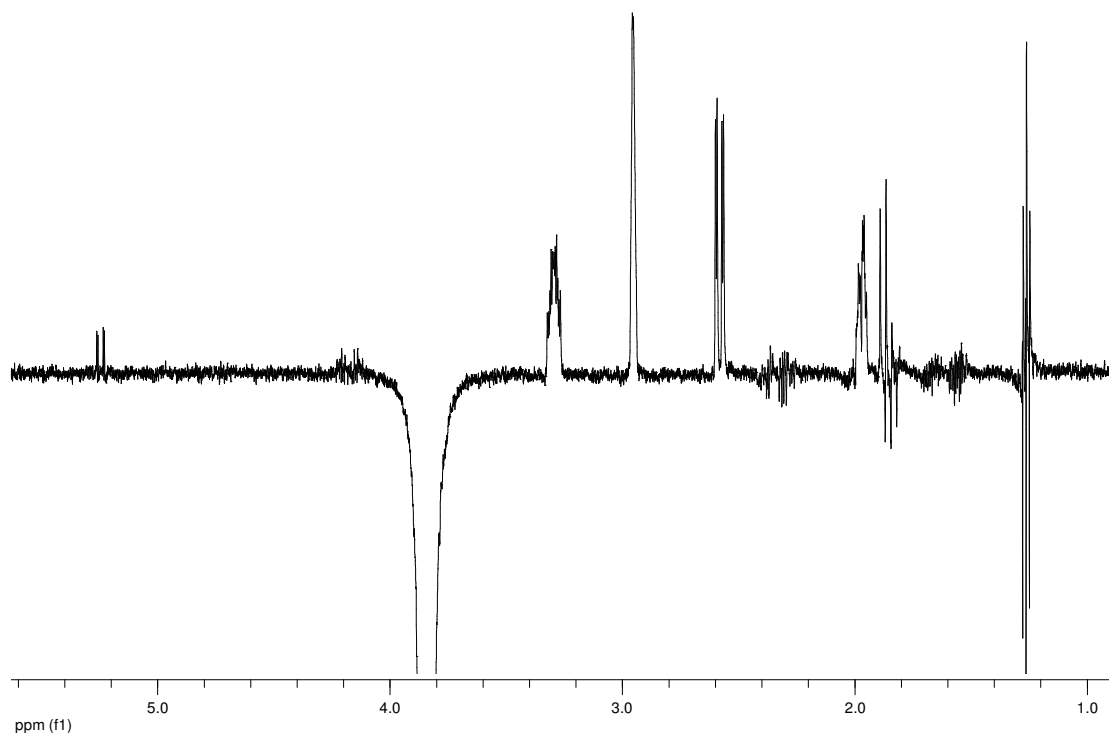


Figure 4.42 ROE spectrum, irradiation of the proton at C8

From figure **4.42**, four protons show ROE signals, these being the protons at $\delta_H = 3.2$, 3.0, 2.6 and 2.0 ppm. The proton at $\delta_H = 3.2$ ppm was previously identified as the ring junction proton and the proton at $\delta_H = 3.0$ ppm as the proton at C7. The proton at $\delta_H = 2.6$ ppm was identified as the axial proton at C6. This leaves one proton at $\delta_H = 2.0$ ppm, which is likely to be the equatorial proton at C9. From these data, the proton at C8 can be assigned the axial position, as only this position gives the required ROE signals. These data also imply that the ring junction is also axial, as this would also give the required ROE signal. Figure **4.43** (below) shows the ROE signals on the structure of compound **4.190**.

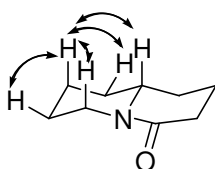


Figure 4.43 ROE signals from irradiating the hydrogen at C8

In order to confirm the stereochemistry of the ring junction proton, a ROE experiment was performed, irradiating the ring junction proton. The spectrum obtained is shown below (Figure **4.44**)

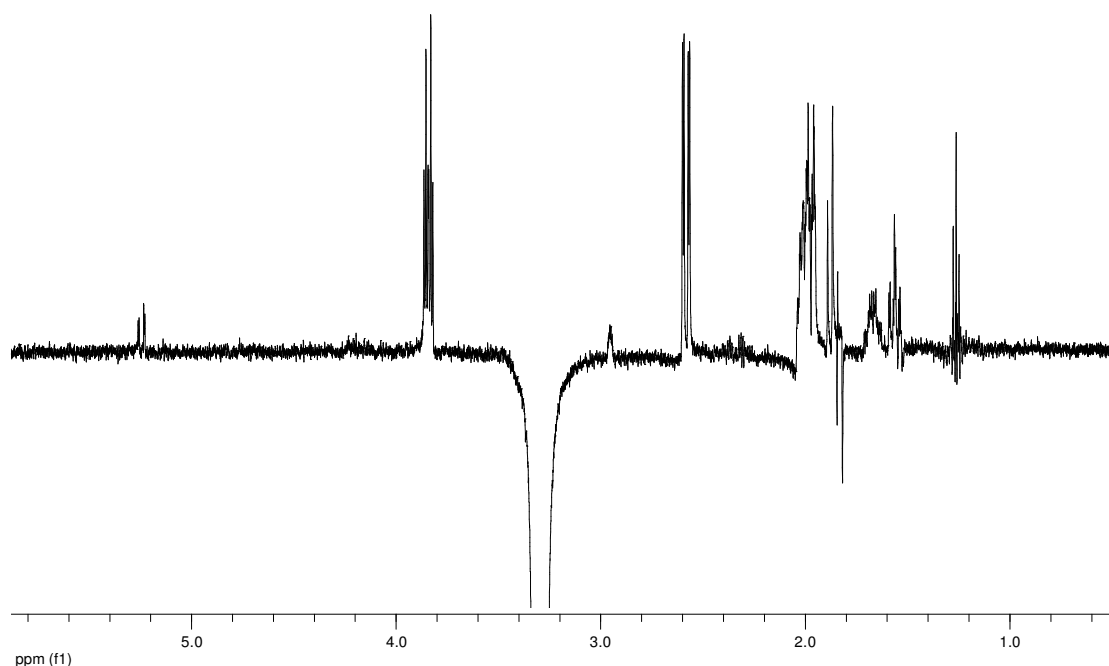


Figure 4.44 ROE spectrum irradiation of the ring junction proton

From figure 4.44, three of the protons that show ROE signals are identifiable as the protons at C8, the axial C6 proton and the equatorial C9 proton. Two others may also be showing signals, potentially the two protons at C1. This experiment confirms that the ring junction proton is axial, again as this is the only position where the proton can give ROE signals to the axial proton at C6. The three main ROE signals for the proton are shown below (Figure 4.45)

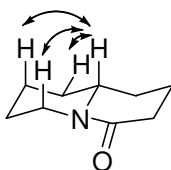


Figure 4.45 ROE signals from irradiating the ring junction proton

With this, the major diastereomer of the hydrogenation was identified with the three hydrogen atoms at the substituted sites all added to the same face. The structure is shown below (Figure 4.46)

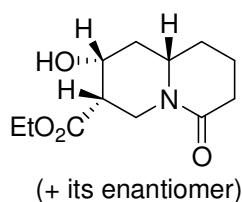


Figure 4.46 Stereochemistry of the major diastereomer **4.190** (Diastereomer 1)

This structure would be expected product, with the hydrogenation reaction occurring on the same face of the molecule. Isolation of the remaining two diastereomers was not possible by column chromatography and it was not possible to assign the stereochemistry from the NMR spectrum of the mixture of diastereomers.

With this result, alternative catalysts and solvents were explored and the effect on the ratio of diastereoisomers observed by ^1H NMR spectroscopy. The other conditions (solvent, pressure) were kept constant and the results are shown in table **4.8** (below)

Catalyst	%Diastereomer1	%Diastereomer2	%Diastereomer3	%Diastereomer4
PtO ₂ /C	73	13	13	0
Pd/C	44	39	17	0
Ru/C	No hydrogenation was observed.			
Rh/C	25	75	0	0
Rh/Al ₂ O ₃	As Rh/C, but with some partial hydrogenated products.			

Table 4.8 Diastereomeric ratios of hydrogenation of compound **4.127**. Ratios were measured based on integrals of the C6 equatorial hydrogen atom, which is observed at $\delta_H = 5.2$ ppm in diastereomer 1, $\delta_H = 5.0$ ppm in diastereomer 2 and $\delta_H = 4.8$ in diastereomer 3.

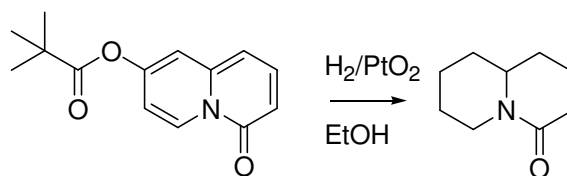
The effect of solvent was also explored using platinum oxide as the catalyst. The results are shown below (table **4.9**)

Solvent	Effect on diastereoselectivity
EtOH	73:13:13:0 (Standard)
EtOAc	No change in diastereoselectivity
DMF	No hydrogenation observed
EtOH/Et ₃ N	No hydrogenation observed

Table 4.9 Effect of solvent on the diastereomeric ratio of the hydrogenation of compound **4.127**

From the four solvents screened, no changes were observed on changing from ethanol to ethyl acetate. The use of DMF, which could be used with the more insoluble 8-hydroxyquinolizinone **4.69**, showed no signs of hydrogenated product. In the presence of an organic base (triethylamine) in ethanol, no sign of hydrogenation was observed.

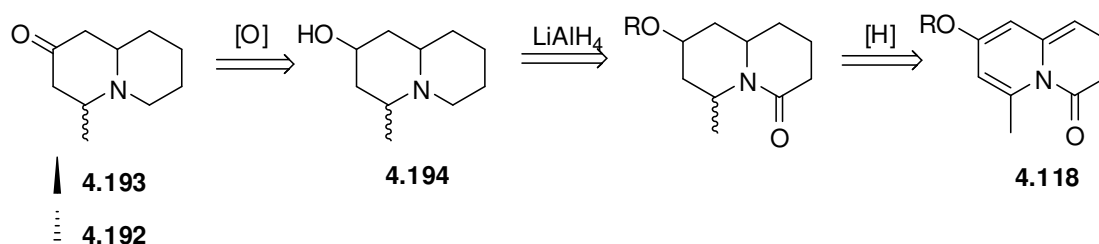
Due to the insolubility of 8-hydroxyquinolizinone **4.69** in alcohol, the trimethylacetyl compound **4.163** was hydrogenated using platinum oxide in ethanol. Upon removal of the catalyst, concentration of the solvent and distillation of the product gave a clear oil. The ¹H NMR spectrum of the product showed that the hydrogenation of the material had gone to completion. However the peak corresponding to the trimethylacetyl group was not present. The ¹³C NMR spectrum also confirmed this, with 7 CH₂, 1 CH and 1 quaternary carbon. The ¹³C NMR spectrum match the literature data for octahydroquinolizinone¹⁰⁷ **4.191**, formed by hydrogenolysis of the trimethylacetoxo group (Scheme **4.115**)



Scheme 4.115 Hydrogenation of compound **4.163**

Although not carried out, further work on the hydrogenation could be applied to a total synthesis of lupinine alkaloids, in particular myrtine **4.192** and epimyrine **4.193**.

The formal retrosynthesis is shown below in scheme **4.116**.



Scheme 4.116 Retrosynthesis of compounds **4.192** and **4.193**

From scheme **4.114**, the natural products can be accessed from compound **4.118**, which has been synthesised by our methodology. The main issue is with the hydrogenation and choosing the appropriate protecting group to allow access to the hydroxyl functionality required in compound **4.194** for the oxidation step. However, this work is beyond the scope of this thesis.

4.3 Conclusion

In this work, a novel rearrangement reaction has been discovered to give a rare heterocyclic ring system, with a substitution pattern which is difficult to obtain by other methodologies. The mechanism of the reaction involves a proton transfer reaction, followed by the formation of a new ketene and subsequent cyclisation. This kind of rearrangement is unusual, but has been shown to be feasible by DFT calculations. The scope of this rearrangement has also been studied and a wide range of substituents were tolerated to give a range of substituted 8-hydroxyquinolizinones.

The reactivity of the ring system was also explored, including the reactivity of the hydroxy group and that of the heterocyclic rings towards electrophiles. The hydroxy group was found to be phenolic-like, as might be expected, and undergoes similar reactions, such as alkylation and acetylation. The compound was found to be highly reactive towards electrophiles, in some examples undergoing multiple substitutions. This allows for new functionality to be easily introduced into the ring system and in some cases, this functionality to be used in further reactions, for example brominated products to be used in palladium catalysed cross coupling reactions.

4.4 Experimental

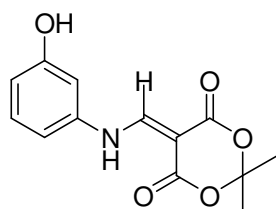
General Method A

The amine (1 equivalent), dissolved in the minimum amount of acetonitrile, was added to a solution of methoxymethylene Meldrum's acid (1 equivalent) in a minimum amount of acetonitrile and allowed to stand for 15 min. Removal of the solvent gave the product.

General Method B

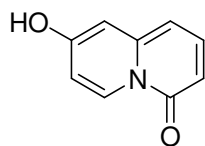
The amine (1 equivalent), dissolved in the minimum amount of acetonitrile, was added to a solution of diethyl ethoxymethylenemalonate (1 equivalent) in a minimum amount of acetonitrile and stirred for 2.5 h at room temperature. Removal of the solvent gave the product.

2,2-Dimethyl-5-[(3-hydroxyphenylamino)methylene]-1,3-dioxane-4,6-dione **4.67**



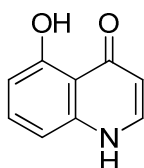
Compound **4.67** was synthesised as previously reported in chapter 3, compound **3.22**, page 135

8-Hydroxyquinolizin-4-one **4.69**



Flash vacuum pyrolysis of compound **4.67** (0.503 mg, T_f 500 °C, T_i 240 °C, P $2.3 - 2.4 \times 10^{-2}$ Torr, t 15 min) gave 8-hydroxyquinolizinone **4.69** as a yellow solid (0.221 g, 72%); mp 242 – 244 °C (from DMF) (Found M^+ 161.04754, $C_9H_7NO_2$ requires 161.04713); δ_H (d_6 -DMSO) 8.96 (1H, d, 3J 8.8), 7.53 (1H, t, 3J 8.0), 6.95 - 6.85 (2H, m), 6.52 (1H, d, 3J 7.8) and 6.04 (1H, dd, 3J 8.8, 4J 1.3) δ_C (d_6 -DMSO) 159.35 (quat), 157.53 (quat), 145.84 (quat), 138.80, 129.70, 111.21, 104.27, 102.01 and 99.89; m/z 161 (M^+ , 27%), 133 (12) and 109 (100).

5-Hydroxyquinolin-4-one **4.68**



Compound **4.67** was synthesised as previously reported in chapter 3, compound **3.53**, page 144

Temperature Profile for the Pyrolysis of 5-[(3-Hydroxyphenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **4.67**

The inlet temperature was set at 240 °C for these pyrolyses:

$T_f/^\circ\text{C}$	wt /mg	$P/\times 10^{-2}$ Torr	t /min	% 4.68	% 4.69
500	49.6	2.6 – 3.0	7	0	100
600	49.6	2.3	11	19	81
700	50.0	2.6 – 2.8	5	43	57
800	49.9	3.0 – 3.6	4	71	29
900	50.5	3.8 – 6.0	5	100	0

Table 4.10 Conditions and results for the pyrolysis of compound **4.67** at various temperatures

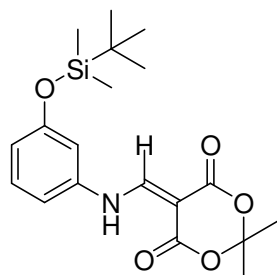
Repyrolysis of 8-Hydroxyquinolizinone **4.69**

The inlet temperature was set at 260 °C for these pyrolyses:

$T_f/^\circ\text{C}$	wt /mg	$P/\times 10^{-2}$ Torr	t /min	% 4.68	% 4.69
600	23.0	2.1 – 2.2	30	0	100
700	25.5	2.3	7	26	74
750	26.5	2.3	8	63	37
800	25.4	2.3	16	82	18
850	26.4	2.6	12	100	0

Table 4.11 Conditions and results for the pyrolysis of compound **4.69** at various temperatures

2,2-Dimethyl-5-[(3-*tert*-butyldimethylsilyloxyphenylamino)methylene]-1,3-dioxane-4,6-dione **4.70**

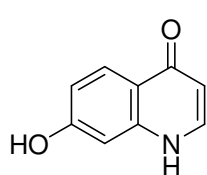


Imidazole (0.68 g 10 mmol) and *tert*-butyldimethylsilyl chloride (1.5 g, 5 mmol) were added to a solution of 5-[(3-hydroxyphenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **4.67** (1.315 g, 5 mmol) in DMF (15 cm³) and the mixture stirred overnight. TLC showed the reaction to be incomplete so a further equivalent of *tert*-butyldimethylsilyl chloride was added and the reaction stirred overnight. The mixture was added to water, extracted with ethyl acetate (3 × 50 cm³), the combined extracts were dried over MgSO₄ and the solvent removed to give a yellow oil, which crystallised upon storage in a freezer. Recrystallisation of the crude material from ethanol gave compound **4.70** as a pale yellow solid (1.10 g, 58%); mp 97 – 99 °C (from ethanol); (Found C, 60.1; H, 7.3; N, 3.7. C₁₉H₂₇NO₅Si requires C, 60.45; H, 7.2; N, 3.7.); δ_H 11.22 (1H, d, br, ³*J* 14.4), 8.65 (1H, d, ³*J* 14.4), 7.31 (1H, t, ³*J* 7.8), 6.89 (1H, dd, ³*J* 7.9, ⁴*J* 2.1), 6.84 – 6.75 (2H, m), 1.80 (6H, s), 1.04 (9H, s) and 0.26 (6H, s); δ_C 165.41 (quat), 163.45 (quat), 157.10 (quat), 152.41, 138.77 (quat), 130.73, 118.30, 110.78, 109.91, 105.05 (quat), 87.04 (quat), 26.90 (2CH₃), 25.45 (3CH₃), 18.02 (quat) and -4.54 (2CH₃); *m/z* 377 (M+H⁺, 40%), 319 (26), 262 (42), 247 (72), 218 (100) and 188 (42).

Pyrolysis of 2,2-Dimethyl-5-[(3-*tert*-butyldimethylsilyloxyphenylamino)methylene]-1,3-dioxane-4,6-dione **4.70**

Pyrolysis of compound **4.70** at 500 °C gave a yellow oil with no identifiable products from the ¹H NMR spectrum of the pyrolysate.

7-Hydroxyquinolin-4-one **4.74**



Hydroiodic Acid (15 cm³) was added dropwise to an ice cooled solution of 7-methoxyquinolinone (0.525 g, 3 mmol) in acetic anhydride (15 cm³). The mixture was heated to reflux for 6 h, then allowed to cool. The mixture was added to a saturated solution of

sodium metabisulfite in water (150 cm³). The aqueous layer was extracted with ethyl acetate (3 × 50 cm³) and the combined extracts dried over MgSO₄. Removal of the solvent gave 7-hydroxyquinolinone **4.74** as a pale brown solid, which was dried under high vacuum (0.193 g, 40%); mp 241 – 242 °C; (Found M⁺ 161.04725, C₉H₇NO₂ requires 161.04713); δ_H 8.65 (1H, d, ³J 6.9), 8.22 (1H, dd, ³J 9.0, ⁴J 2.9), 7.36 (2H, m) and 6.89 (1H, d, ³J 6.9); δ_C 172.36 (quat), 170.45 (quat), 162.97 (quat), 144.11, 142.19 (quat), 126.24, 119.53, 104.55, 101.84; *m/z* 161 (M⁺, 18%), 128 (100) and 142 (13).

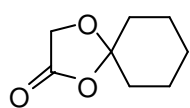
Pyrolysis of Quinolinols

Pyrolysis of 5-Hydroxyquinoline

FVP of 5-hydroxyquinoline (30.1 mg, *T_f* 750 °C, *T_i* 180 °C, *P* 2.6 × 10⁻² Torr, *t* 10 min) returned only starting material by ¹H NMR spectroscopy.

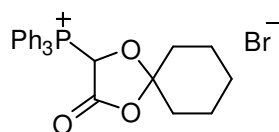
FVP of 5-hydroxyquinoline at a higher temperature (30.0 mg, *T_f* 900 °C, *T_i* 180 °C, *P* 3.8 – 4.4 × 10⁻² Torr, *t* 14 min) returned only starting material by ¹H NMR spectroscopy.

1,4-Dioxaspiro[4,5]decan-2-one⁸⁵ **4.95**



A solution of cyclohexanone (21.7 g, 0.22 mol) and *p*-toluenesulfonic acid (0.05 g, 0.03 mmol) in toluene (100 cm³) was heated to reflux and a solution of glycolic acid (13.6 g, 0.18 mol) in water (10 cm³) was added over 3 h. The reaction was heated for a further 4 h and water (15.4 cm³) was removed using a Dean-Stark trap. The reaction mixture was cooled to room temperature, anhydrous sodium acetate (0.083 g) added and the mixture stirred for 1 h. The solid was filtered off and the solvent removed to give a yellow oil. Purification by Kugelrohr distillation gave compound **4.95** as a clear oil (14.87 g, 43%); δ_H 2.34 (2H, s), 2.00 – 1.20 (8H, m). NMR data matches literature spectrum.⁸⁵

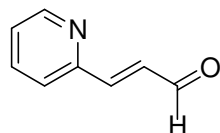
(3-Oxo-1,4-dioxaspiro[4.5]dec-2-yl)triphenylphosphonium bromide⁸⁵ **4.92**



A solution of 1,4-Dioxaspiro[4,5]decan-2-one **4.95** (2.02 g, 13 mmol), AIBN (0.032 g) and *N*-bromosuccinimide (2.93 g, 16.5 mmol) in carbon tetrachloride (40 cm³) was heated to reflux under a 100 W lamp. Initially an orange solution formed, quickly followed by solution turning colourless. ¹H NMR spectroscopy showed the reaction to be incomplete and further portions of AIBN (0.032 g) and *N*-bromosuccinimide (1.26 g, 7 mmol) were added. The reflux maintained for a further 1 h and the reaction was complete by ¹H NMR spectroscopy. The mixture was cooled, the solid filtered off and the solution concentrated to give a brown oil.

The brown oil was dissolved in toluene (10 cm³) and a solution of triphenylphosphine (3.7 g) in toluene (30 cm³) was added dropwise over 1 h. The mixture was stirred overnight and the white solid filtered off (4.52 g, 70%); δ_H (*d*₆-Acetone) 8.10 – 7.80 (16H, m) and 2.30 – 1.20 (10H, m). NMR data matches literature spectrum.⁸⁵

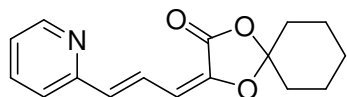
3-(Pyridin-2-yl)-propenal **4.93**



Triethylamine (4 cm³) was added to a suspension of (formylmethyl)triphenylphosphonium chloride ((3.75 g, 10 mmol) in toluene (180 cm³) and the mixture stirred for 0.5 h. 2-Pyridinecarboxaldehyde (1.05 g, 10 mmol) was added and the mixture stirred overnight at room temperature. DCM and water were added, the organics separated off, dried over MgSO₄ and the solvent removed to give a black oil. Purification by column chromatography (silica, ethyl acetate/hexane, 1:1) gave 3-(pyridin-2-yl)-propenal **4.93** as a brown solid (9:1 mixture of isomers, 1.01 g, 77%); mp 52 -54 °C (hexane; lit.,¹⁰⁸ 47 °C); δ_H (Major isomer) 9.57 (1H, d, ³*J* 7.8), 8.45 (1H, ddd, ³*J* 4.8, ⁴*J* 2.0, ⁵*J* 1.0), 7.53 (1H, td, ³*J* 7.5, ⁴*J* 1.0), 7.33 – 7.29 (2H, m), 7.07 (1H, ddd, ³*J* 7.8, ⁴*J* 3.0, ⁵*J* 1.3) and 6.85 (1H, dd, ³*J* 15.8, ⁴*J* 7.8); δ_C (Major Isomer) 193.48 (quat), 152.48 (quat), 151.03, 150.22, 136.74, 131.42, 124.76 and 124.11; δ_H (Minor Isomer) 9.42 (1H, d, ³*J* 7.8), 8.39 (1H, m), 7.60 (1H, dd, ³*J* 7.8, ⁴*J* 1.8), 7.31 (1H, dt, ³*J* 7.8, ⁴*J* 1.0), 7.08 - 7.06 (2H, m) and 6.10 (1H, dd, ³*J* 15.0, ⁴*J* 7.8); δ_C (Minor Isomer) 153.59 (quat), 150.73, 149.91, 140.63, 133.27,

129.70 and 123.47, one quat not apparent.

3-[3-Pyridin-2-yl-prop-2-enylidene]-1,4-dioxo-spiro[4.5]decan-2-one **4.91**



(3-Oxo-1,4-dioxo-spiro[4.5]decan-2-yl)triphenylphosphonium bromide **4.92** (0.496 g, 1 mmol) in toluene (5 cm³) was heated to reflux and 1,4-diazabicyclo[2.2.2]octane (1.05 mmol) in toluene (6 cm³) was added. The mixture was stirred for 5 min and 3-(pyridin-2-yl)-propenal **4.93** (0.133 g, 1 mmol) in toluene (5 cm³) was added. The mixture was refluxed for 1h, cooled to room temperature and the solid diazabicyclooctane HBr salt filtered off. The solvent was removed and the product purified by column chromatography to give 3-[3-pyridin-2-yl-prop-2-enylidene]-1,4-dioxo-spiro[4.5]decan-2-one **4.91** as a inseparable mixture of isomers (0.091 g, 19%); δ_H (Minor isomer, 360 MHz) 8.58 (1H, ddd, 3J 4.7, 4J 1.6, 5J 0.7), 7.65 (1H, dd, 3J 7.9, 4J 1.8), 7.60 (1H, dd, 3J 7.8, 4J 1.8), 7.52 (1H, dd, 3J 15.5, 4J 11.7), 7.32 (1H, d, 3J 7.2), 6.82 (1H, d, 3J 15.5), 6.33 (1H, dd, 3J 11.7, 4J 0.8) and 2.00 – 1.35 (10H, m); δ_H (Major isomer, 360 MHz) 8.55 (1H, ddd, 3J 4.7, 4J , 5J 0.9), 8.17 (1H, dd, 3J 15.7, 4J 11.9), 7.47 (1H, dt, 3J 8.0, 4J 2.0), 7.14 (1H, ddd, 3J 7.5, 4J 4.8, 5J 1.1), 7.10 (1H, ddd, 3J 7.5, 4J 4.9, 5J 1.1), 6.73 (1H, d, 3J 15.6), 6.31 (1H, dd, 3J 11.9, 4J 0.9) and 2.00 – 1.35 (10H, m).

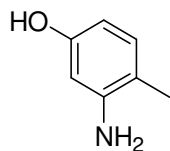
Pyrolysis of 3-[3-Pyridin-2-yl-prop-2-enylidene]-1,4-dioxo-spiro[4.5]decan-2-one

Pyrolysis of compound **4.91** (w 0.102 g, T_f 600 °C, T_i 140 °C, P 2.6 – 7.5 $\times 10^{-2}$ Torr, t 20 min) gave a brown solid and an oil. Purification of the mixture by column chromatography gave quinolizin-4-one **4.81** as a brown solid (0.043 g, 70%); δ_H (360 MHz) 9.13 (1H, d, 3J 7.4), 7.66 (1H, dd, 3J 8.8, 4J 7.7), 7.47 (1H, d, 3J 8.8), 7.33 (1H, ddd, 3J 8.8, 4J 6.6, 5J 1.1), 7.00 (1H, t, 3J 7.7) 6.66 (1H, d, 3J 7.8) and 6.63 (1H, d, 3J 9.0); δ_C (90 MHz) 158.51 (quat), 142.52 (quat), 137.99, 129.19, 127.14, 125.27, 114.95, 108.94 and 103.28. NMR data matches literature spectrum.⁸⁷

Solution Phase Pyrolysis of 2,2-Dimethyl-5-[(3-hydroxyphenylamino)methylene]-1,3-dioxane-4,6-dione **4.67**

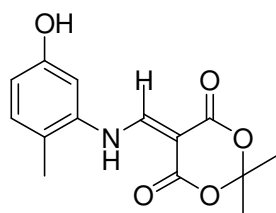
Compound **4.97** (0.1 g) was added to a refluxing solution of Dowtherm A (5 cm³) and the heating maintained for 20 min. Addition of petroleum ether caused the precipitation of a brown solid, which was filtered off and washed with petroleum ether. The ¹H NMR spectrum showed a mixture of 5-hydroxy- and 7-hydroxyquinolinones in a 60:40 ratio.

3-Amino-*p*-cresol **4.100**



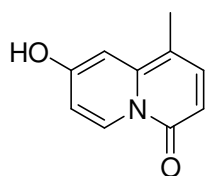
4-Methyl-3-nitrophenol (1.00 g, 6.54 mmol) in ethyl acetate (30 cm³) was hydrogenated over Pd/C (28 mg) at 10 bar for 3 h. The solution was filtered through celite and removal of the solvent gave a white powder (0.808 g quant.) mp 160 – 162 °C (lit.,¹⁰⁹ 160 °C); δ_H (*d*₆-DMSO) 8.64 (1H, s), 6.66 (1H, d, ³*J* 8.0), 6.07 (1H, d, ⁴*J* 2.4), 5.89 (1H, dd, ³*J* 8.0, ⁴*J* 2.4), 4.65 (2H, s) and 1.93 (3H, s); δ_C (*d*₆-DMSO) 157.07 (quat), 148.20 (quat), 131.15, 112.73 (quat), 104.35, 102.09 and 17.56 (CH₃).

2,2-Dimethyl-5-[(3-hydroxy-6-methylphenylamino)methylene]-1,3-dioxane-4,6-dione **4.105**



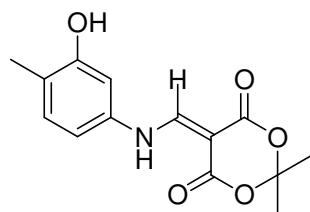
Using general method A, 3-amino-*p*-cresol (0.550 g, 5 mmol) gave 2,2-dimethyl-5-[(3-hydroxyphenylamino)methylene]-1,3-dioxane-4,6-dione **4.105** as a yellow solid (1.376 g, 99%) mp 209 – 211 °C (from ethanol); (Found C, 60.55; H, 5.35; N, 5.05. C₁₄H₁₅NO₅ requires C, 60.65; H, 5.4; N, 5.05 %); δ_H (*d*₆-DMSO) 11.23 (1H, d, ³*J* 14.1), 9.58 (1H, s), 8.49 (1H, d, ³*J* 14.1), 7.09 (1H, d, ³*J* 8.3), 6.93 (1H, d, ⁴*J* 2.3), 6.62 (1H, dd, ³*J* 8.3, ⁴*J* 2.3), 2.21 (3H, s) and 1.68 (6H, s); δ_C 165.81 (quat), 157.66 (quat), 154.03, 138.03 (quat), 132.72, 118.83 (quat), 114.49, 105.31 (quat), 104.98, 87.48 (quat), 27.36 (2CH₃) and 16.76 (CH₃); *m/z* 277 (M⁺, 30%), 219 (76), 201 (100), 174 (64), 160 (83) and 146 (69).

8-Hydroxy-1-methylquinolizin-4-one **4.109**



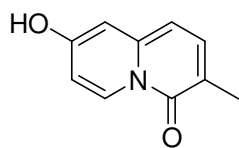
Pyrolysis of compound **4.105** (w 0.502 g, T_f 500 °C, T_i 190 °C, P 2.3×10^{-2} Torr, t 48 min) gave a yellow solid (0.201 g, 64%), which was heated in methanol and filtered when cold to give a pure sample of 8-Hydroxy-1-methylquinolizin-4-one **4.109** (0.104 g, 32%); mp 244 - 246 °C; (Found M^+ 175.06262, $C_{10}H_9NO_2$ requires 175.06278) δ_H (d_6 -DMSO) 9.02 (1H, d, 3J 7.9), 7.43 (1H, d, 3J 8.6), 6.89 (1H, dd, 3J 7.6, 4J 2.5), 6.88 (1H, d, 4J 2.5), 5.98 (1H, d, 3J 8.6) and 2.21 (3H, s); δ_C (90 MHz, d_6 -DMSO) 158.93 (quat), 156.48 (quat), 143.01 (quat), 140.07, 130.08, 110.20, 104.49 (quat), 101.35, 100.72 and 16.55 (CH_3); m/z 175 (M^+ , 74%), 147 (44), 146 (100), 120 (25), 111 (22) and 109 (20).

2,2-Dimethyl-5-[(3-hydroxy-4-methylphenylamino)methylene]-1,3-dioxane-4,6-dione **4.104**



Using general method A, 5-amino-*o*-cresol (0.550 g, 5 mmol) gave 2,2-dimethyl-5-[(3-hydroxyphenylamino)methylene]-1,3-dioxane-4,6-dione **4.104** as a yellow solid (1.219 g, 88%); mp 223 - 225 °C (from ethyl acetate); (Found M^+ 277.09476, $C_{14}H_{15}NO_5$ requires 277.09447); δ_H (360 MHz, d_6 -DMSO) 11.10 (1H, d, 3J 14.7), 9.70 (1H, s), 8.42 (1H, d, 3J 14.7), 7.10 (1H, d, 3J 8.1), 6.87 (1H, d, 3J 8.1), 8.41 (1H, s), 2.10 (3H, s) and 1.66 (6H, s); δ_C (90 MHz, d_6 -DMSO) 163.99 (quat), 162.96 (quat), 156.22 (quat), 152.66, 137.20 (quat), 131.45, 122.69 (quat), 109.45, 105.10, 104.21 (quat), 86.15 (quat), 26.55 (2 CH_3) and 15.60 (CH_3); m/z 277 (M^+ , 36%), 267 (69), 255 (24), 219 (78), 174 (70), 160 (100), 146 (66) and 123 (34)

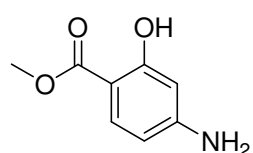
8-Hydroxy-3-methylquinolizin-4-one **4.108**



Flash vacuum pyrolysis of compound **4.104** (w 0.500 g, T_f 500 °C, T_i 200 °C, P $2.3 - 2.9 \times 10^{-2}$ Torr, t 55 min) gave a yellow solid (0.361 g), which can be recrystallised from DMF to give a pure

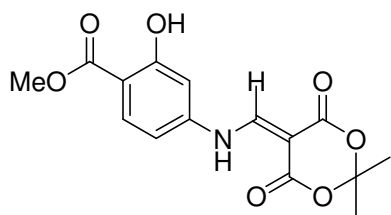
sample of 8-hydroxy-3-methylquinolizin-4-one **4.108** (0.067 g, 21%). mp 229 – 231 °C; (Found M^+ 175.06213, $C_{10}H_9NO_2$ requires 175.06278); δ_H (d_6 -DMSO) 11.06 (1H, s, br), 8.90 (1H, d, 3J 8.8), 7.48 (1H, d, 3J 7.8), 6.82 – 6.78 (2H, m), 6.42 (1H, d, 3J 8.0) and 2.12 (3H, s); δ_C (d_6 -DMSO) 157.22 (quat), 157.12 (quat), 143.10 (quat), 137.61, 128.58, 110.73 (quat), 110.63, 103.35, 98.48 and 16.68 (CH_3); m/z 175 (M^+ , 100%), 146 (72) and 117 (8).

Methyl 4-aminosalicylate¹⁰⁸ **4.101**



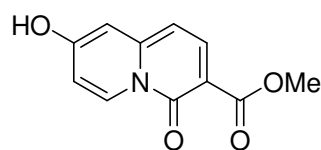
Concentrated sulfuric acid (14 cm³) was added to a solution of 4-aminosalicylic acid (10.00 g, 65.4 mmol) in methanol (200 cm³) and heated to reflux overnight. The mixture was allowed to cool and sat. $NaHCO_3$ was added until the acid was neutralised and a brown precipitate formed. methyl 4-aminosalicylate **4.101** was obtained by filtration (8.75 g, 80%); mp 120 – 122 °C (lit.,¹¹⁰ 120 – 121 °C) δ_H (d_6 -DMSO) 10.86 (1H, s), 7.52 (1H, d, 3J 8.7), 6.22 – 6.18 (3H, m), 6.08 (1H, d, 3J 2.1) and 3.86 (3H, s); δ_C (d_6 -DMSO) 170.27 (quat), 163.21 (quat), 156.37 (quat), 131.37, 106.98, 99.91 (quat), 98.91 and 51.85 (CH_3)

2,2-Dimethyl-5-[(3-hydroxy-4-carbomethoxyphenylamino)methylene]-1,3-dioxane-4,6-dione **4.107**



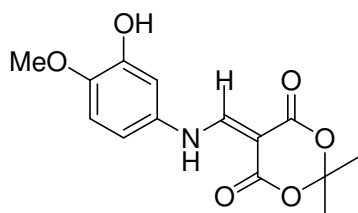
Using general method A, methyl 4-aminosalicylate (0.835 g, 5 mmol) gave 2,2-Dimethyl-5-[(3-hydroxy-4-carbomethoxyphenylamino)methylene]-1,3-dioxane-4,6-dione **4.107** as a yellow solid (1.588 g, 99%); mp 205 – 207 °C (from ethanol); (Found C, 56.0; H, 4.4; N, 4.25. $C_{15}H_{15}NO_7$ requires C, 56.05; H, 4.7; N, 4.35.); δ_H (360 MHz) 11.18 (1H, d, br 3J 14.0), 10.98 (1H, s), 8.65 (1H, d, 3J 14.0), 7.89 (1H, d, 3J 8.6), 6.83 (1H, d, 3J 2.3), 6.75 (1H, dd, 3J 8.6, 4J 2.3), 3.96 (3H, s) and 1.72 (6H, s); δ_C (90 MHz) 169.53 (quat), 165.16 (quat), 162.99, 162.94 (quat), 151.70, 143.26 (quat), 132.05, 110.39 (quat), 108.41, 105.61, 105.34 (quat), 88.74 (quat), 52.37 (CH_3) and 27.01 (2 CH_3); m/z 321 (M^+ , 38%), 263 (61), 218 (100), 187 (25), 159 (66).

3-Carbomethoxy-8-hydroxyquinolizinone **4.111**



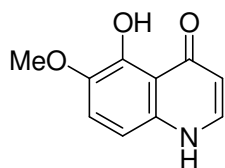
Pyrolysis of compound **4.107** (w 0.20 g, T_f 500 °C, T_i 180, P $1.3 - 1.4 \times 10^{-7}$ Torr, t 1 h 50 min) gave 3-carbomethoxy-8-hydroxyquinolizinone **4.111** as a yellow solid (0.057 g, 42%); mp 240 – 241 °C (decomp); [Found (M+H)⁺ 220.06010, C₁₁H₁₀NO₄ requires 220.06043]; δ_H (d_6 -DMSO, 500 MHz) 9.22 (1H, d, 3J 7.5), 8.08 (1H, d, 3J 8.6), 7.12 – 7.07 (2H, m), 6.60 (1H, d, 3J 9.0) and 3.77 (3H, s); δ_C (d_6 -DMSO, 125 MHz) 166.30 (quat), 163.66 (quat), 154.78 (quat), 149.08 (quat), 139.49, 132.05, 111.73, 105.66, 100.25, 98.90 (quat) and 51.13 (CH₃); m/z (+ve ESI) 220 [(M+H)⁺, 31%].

2,2-Dimethyl-5-[(3-hydroxy-4-methoxyphenylamino)methylene]-1,3-dioxane-4,6-dione **4.106**



Using general method A; 5-amino-2-methoxyphenol (1.252 g, 9 mmol) gave 2,2-dimethyl-5-[(3-hydroxy-4-methoxyphenylamino)methylene]-1,3-dioxane-4,6-dione **4.106** as a yellow solid (2.654 g, quant.); mp 195 – 197 °C (from ethanol); (Found C, 57.45; H, 5.05; N, 4.65. C₁₄H₁₅NO₆ requires C, 57.35; H, 5.1; N, 4.8); δ_H 11.17 (1H, br, d, 3J 14.4), 8.57 (1H, d, 3J 14.4), 6.92 (1H, d, 3J 2.7), 6.87 (1H, d, 3J 8.6), 6.72 (1H, dd, 3J 8.6, 4J 2.7), 3.92 (3H, s) and 1.75 (6H, s); δ_C 165.52 (quat), 152.53 (quat), 146.89, 145.55 (quat), 131.68 (quat), 111.23, 109.81, 104.98 (quat), 104.79, 56.15 (CH₃) and 26.88 (2CH₃); m/z 293 (M⁺, 20%), 268 (25), 252 (100), 235 (36), 191 (71) and 148 (70).

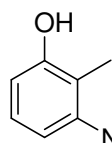
5-Hydroxy-6-methoxyquinolin-4-one **4.110**



Pyrolysis of compound **4.106** (w 0.5104 g, T_f 600 °C, T_i 180 °C, P $2.3 - 2.4 \times 10^{-2}$ Torr, t 40 min.) gave 5-hydroxy-6-methoxyquinolinone **4.110** as a dark brown solid (0.2133 g, 64%); mp 220 – 222 °C (from ethanol); (Found M⁺ 191.05785, C₁₀H₉NO₃ requires 191.05769); δ_H (d_6 -DMSO) 8.01 (1H, d, 3J 7.4), 7.45 (1H, d, 3J 9.0), 6.98 (1H, d, 3J

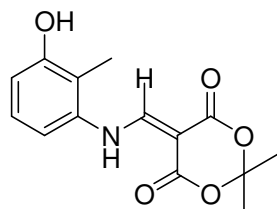
9.0), 6.06 (1H, d, 3J 7.2) and 3.85 (3H, s); δ_C (d_6 -DMSO) 182.60 (quat), 149.71 (quat), 141.34 (quat), 141.09, 135.10 (quat), 120.88, 114.11 (quat), 107.15, 106.22 and 57.11 (CH₃)

3-Amino-*o*-cresol **4.113**



2-Methyl-3-nitrophenol (0.383 g, 2.5 mmol), Pd/C (40 mg) in ethanol (50 cm³) were placed in a three necked 250 cm³ round bottomed flask. The system was purged under vacuum and nitrogen charged. The system was then purged again and hydrogen charged *via* a balloon and the solution stirred under a hydrogen atmosphere for 2 h. The solution was then filtered through celite and the solution concentrated to give 3-amino-*o*-cresol **4.113** as a purple solid (0.302 g, 98%); mp 131 – 133 °C (lit.,⁸⁷ 129 – 130 °C); δ_H 6.80 (1H, t, 3J 8.0), 6.25 (1H, d, 3J 7.9), 6.17 (1H, d, 3J 8.0) and 1.99 (3H, s).

2,2-Dimethyl-5-[(3-hydroxy-2-methylphenylamino)methylene]-1,3-dioxane-4,6-dione **4.114**



Using general method A, 3-amino-*o*-cresol (0.246 g, 2 mmol) gave 2,2-dimethyl-5-[(3-hydroxy-2-methylphenylamino)methylene]-1,3-dioxane-4,6-dione **4.114** as an off-yellow solid (0.557 g, quant.); mp 220 – 222 °C (from ethanol); (Found M^+ 277.09403, C₁₄H₁₅NO₅ requires 277.09447); δ_H (d_6 -DMSO) 11.33 (1H, br, d, 3J 14.3), 9.81 (1H, s), 8.54 (1H, d, 3J 14.3), 7.15 – 7.03 (2H, m), 6.76 (1H, dd, 3J 7.4, 4J 1.6), 2.13 (3H, s) and 1.68 (6H, s); δ_C (d_6 -DMSO) 164.84 (quat), 162.44 (quat), 155.90 (quat), 153.71, 137.74 (quat), 127.14, 114.83 (quat), 112.88, 108.30, 104.27 (quat), 86.37 (quat), 26.37 (2CH₃) and 9.27 (CH₃); m/z 277 (M^+ , 57%), 219 (100), 174 (20), 160 (38) and 147 (65).

Pyrolysis of 2,2-Dimethyl-5-[(3-hydroxy-2-methylphenylamino)methylene]-1,3-dioxane-4,6-dione **4.114**

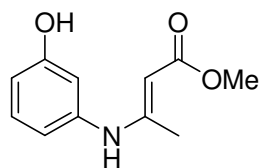
Pyrolysis of compound **4.114** (w 0.284 g, T_f 500 °C, T_i 240 °C, P 3.2 – 4.8 × 10⁻² Torr,

t 15 min) gave a off-yellow solid (0.125 g, 70%). The ^1H NMR spectrum of the crude material showed a 4:1 mixture of 8-hydroxy-9-methylquinolizin-4-one **4.115** and 7-hydroxy-8-methylquinolin-4-one **4.116**, which were inseparable by column chromatography or recrystallisation.

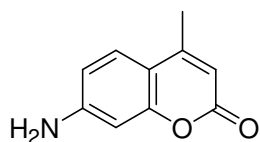
8-Hydroxy-9-methylquinolizin-4-one **4.115** δ_{H} (d_6 -DMSO) 9.00 (1H, d, 3J 8.0), 7.64 (1H, t, 3J 8.5), 7.02 (1H, d, 3J 8.0), 6.55 (1H, d, 3J 8.0), 6.14 (1H, d, 3J 8.5) and 2.27 (3H, s).

7-Hydroxy-8-methylquinolin-4-one **4.116** δ_{H} (d_6 -DMSO) 7.88 (1H, d, 3J 8.9), 7.77 (1H, t, 3J 7.1), 6.92 (1H, d, 3J 8.9), 6.09 (1H, d, 3J 7.1) and 2.29 (3H, s).

Methyl 3-(3-hydroxyphenylamino)-but-2-enoate **4.117**

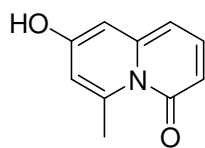


A solution of 3-aminophenol (4.36 g, 40 mmol), methyl acetoacetate (4.6 cm³) and acetic acid (10 drops) in methanol (40 cm³) were heated at reflux for 3 h. The solvent was removed and the product dissolved in dichloromethane (100 cm³), washed with a solution of CuSO₄·5H₂O (2 g in 100 cm³ H₂O) and dried over MgSO₄. Removal of the solvent gave methyl 3-(3-hydroxyphenylamino)-but-2-enoate **4.117** as an off-white solid (7.39 g, 89%) mp 68-69 °C (from toluene); (Found C, 64.1; H, 6.1; N, 6.8. C₁₁H₁₃NO₃ requires C, 63.75; H, 6.3; N, 6.75 %); δ_{H} 10.24 (1H, s, br), 7.17 (1H, t, 3J 8.3), 6.70 (1H, s, br), 6.67 – 6.61 (3H, m), 4.72 (1H, s), 3.74 (3H, s) and 2.01 (3H, s); δ_{C} 171.20 (quat), 159.83 (quat), 156.71 (quat), 139.98 (quat), 129.97, 116.57, 112.51, 111.41, 85.24, 50.55 (CH₃) and 20.24 (CH₃); *m/z* 207 (M⁺, 100%), 176 (22), 148 (80), 147 (95) and 134 (42).



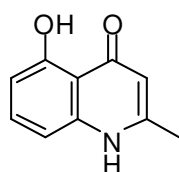
If too much acetic acid is added to the reaction mixture, the product is 7-amino-4-methylcoumarin; mp 225 – 226 °C (from ethanol, lit.,¹¹¹ 222 °C); δ_{H} (360 MHz, d_6 -DMSO) 7.39 (1H, d, 3J 8.6), 6.56 (1H, dd, 3J 8.6, 4J 2.2), 6.40 (1H, d, 4J 2.2), 6.12 (2H, s, br), 5.90 (1H, s) and 2.11 (3H, s); δ_{C} (90 MHz, d_6 -DMSO) 162.24 (quat), 156.92 (quat), 155.26 (quat), 154.55 (quat), 127.69, 112.64, 110.31 (quat), 108.93, 99.97 and 19.50 (CH₃).

8-Hydroxy-6-methylquinolizin-4-one **4.118**



Pyrolysis of compound **4.117** (w 2.051 g, T_f 450 °C, T_i 140 °C, P 2.3 – 3.0×10^{-2} Torr, t 45 min.) gave a brown solid (1.6743 g) which was purified by heating in methanol to give 8-hydroxy-6-methylquinolizin-4-one **4.118** as a yellow-brown solid (0.794 g, 47%); mp 199 – 203 °C (decomp.) [Found (M-H)⁻ 174.05464, C₁₀H₈NO₂ requires 174.05496]; δ_H 10.98 (1H, s, br), 7.39 (1H, t, 3J 8.4), 6.64 (1H, d, 3J 2.6), 6.46 (1H, d, 3J 1.8), 6.33 (1H, dd, 3J 7.5, 4J 1.2), 5.91 (1H, dd, 3J 8.6, 4J 1.2) and 2.94 (3H, s); δ_C 162.14 (quat), 157.68 (quat), 148.26 (quat), 145.33 (quat), 138.12, 113.78, 105.47, 103.15, 100.22 and 24.92 (CH₃); m/z 175 (M⁺, 22%), 174 (100), 161 (39), 149 (41) 133 (43), 105 (36) and 91 (86).

5-Hydroxy-2-methylquinolin-4-one **4.119**



Pyrolysis of compound **4.117** (w 1.138 g, T_f 700 °C, T_i 120 °C, P 2.9 – 5.0×10^{-2} Torr, t 50 min.) gave 5-hydroxy-2-methylquinolin-4-one **4.119** as a yellow solid (0.278 g, 30%); mp 226 – 228 °C (lit.,¹¹² 243 °C from ethanol); δ_H 14.60 (1H, s), 12.03 (1H, s), 7.47 (1H, t, 3J 8.1), 6.89 (1H, d, 3J 8.3), 6.54 (1H, d, 3J 8.0), 5.99 (1H, s) and 2.37 (3H, s); δ_C 181.87 (quat), 161.08 (quat), 151.78 (quat), 140.92 (quat), 133.52, 111.85 (quat); 107.50, 106.85, 106.33 and 19.46 (CH₃); m/z 175 (M⁺, 100%), 152 (26) and 147 (33).

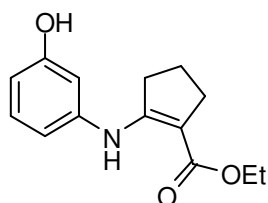
Temperature Profile data for the Pyrolysis of compound 4.117

The inlet temperature for these reaction was set for 140 °C

w /mg	$T_f/^\circ\text{C}$	$P \quad / \times 10^{-2}$	T /min	%4.117	%4.118	%4.119
100.8	350	3.2 – 3.6	8	100	0	0
104.3	400	2.6 – 2.8	5	63	37	0
101.3	450	2.8 – 3.4	6	37	76	3
99.8	500	2.6 – 2.7	6	11	78	11
103.4	550	2.5 – 3.0	7	11	51	38
99.5	600	2.3 – 2.6	5	13	13	74
100.0	700	2.6 – 2.9	5	9	0	91

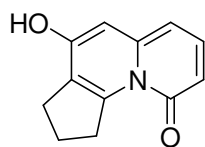
Table 4.12 Conditions and results for the pyrolysis of compound **4.117** at various temperatures

Ethyl 2-(3-hydroxyphenylamino)-cyclopent-1-ene carboxylate 4.122



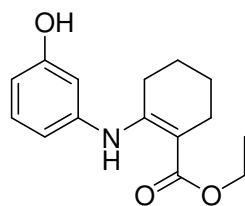
A solution of 3-aminophenol (1.09 g, 10 mmol), ethyl 2-oxocyclopentanecarboxylate (1.56 g, 10 mmol) and acetic acid (5 drops) in ethanol (10 cm³) was heated at reflux for 3 h. The solvent was removed and the product dissolved in dichloromethane, washed with a CuSO₄·5H₂O solution (0.5 g in 50 cm³), water and dried over MgSO₄. Removal of the solvent gave ethyl 2-(3-hydroxyphenylamino)-cyclopent-1-ene carboxylate **4.122** as a brown solid (2.27 g, 92%); mp 109 – 111 °C (from toluene); (Found C, 67.9; H, 6.9; N, 5.55. C₁₄H₁₇NO₃ requires C, 68.05; H, 6.9; N, 5.65 %); δ_H 9.47 (1H, s) 7.10 (1H, t, ³J 7.7), 6.66 (1H, s), 6.60 – 6.51 (3H, m), 4.20 (2H, q, ³J 7.1), 2.78 (2H, t, ³J 7.5), 2.56 (2H, t, ³J 7.0), 1.85 (2H, pentet, ³J 7.6) and 1.31 (3H, t, ³J 7.1); δ_C 168.93 (quat), 161.10 (quat), 158.85 (quat), 141.65 (quat), 130.06, 113.07, 110.62, 107.98, 97.52 (quat), 59.39 (CH₂), 33.76 (CH₂), 28.07 (CH₂), 21.75 (CH₂) and 14.55 (CH₃); m/z 247 (M⁺, 78%), 201 (21), 173 (100), 166 (42) and 150 (12)

4-Hydroxy-2,3-dihydro-1*H*-9a-azabenz[*e*]inden-9-one **4.124**



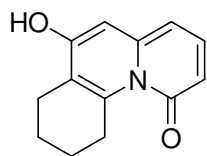
Pyrolysis of compound **4.112** (w 0.501 g, T_f 500 °C, T_i 140 °C, P 2.3 – 2.5×10^{-2} Torr, t 50 min) gave a pale yellow solid (0.428 g), which was purified by heating in methanol to give 4-hydroxy-2,3-dihydro-1*H*-9a-azabenz[*e*]inden-9-one **4.124** as a pale yellow solid (0.332 g, 81%); mp 275 – 277 °C (decomp.); (Found M^+ 201.07827, $C_{12}H_{11}NO_2$ requires 201.07843) δ_H (d_6 -DMSO, 360 MHz) 7.30 (1H, t, 3J 7.6), 6.60 (1H, s), 6.30 (1H, dd, 3J 7.9, 4J 1.4), 5.79 (1H, dd, 3J 8.6, 4J 1.4), 3.88 (2H, t, 3J 7.6), 2.69 (2H, t, 3J 7.2) and 2.00 (2H, p, 3J 7.9); δ_C (d_6 -DMSO, 90 MHz) 160.44 (quat), 157.15 (quat), 147.82 (quat), 147.32 (quat), 137.38, 124.86 (quat), 103.53, 102.88, 99.73, 36.24 (CH_2), 26.47 (CH_2) and 22.46 (CH_2); m/z 201 (M^+ , 81%), 173 (100), 172 (51) and 144 (11).

Ethyl 2-(3-hydroxyphenylamino)-cyclohex-1-ene carboxylate **4.123**



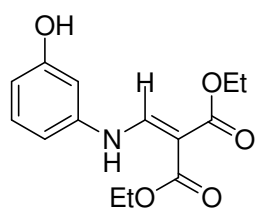
A solution of 3-aminophenol (1.09 g, 10 mmol), ethyl cyclohexanone-2-carboxylate (1.6 cm³) and acetic acid (5 drops) in ethanol (10 cm³) were heated to reflux for 3h. The mixture was cooled, the solvent removed under vacuum and the yellow oil redissolved in DCM. The DCM was washed with a solution of $CuSO_4 \cdot 5H_2O$ (0.5 g, 50 cm³), brine and dried over $MgSO_4$. Removal of the solvent gave ethyl 2-(3-hydroxyphenylamino)-cyclohex-1-ene carboxylate **4.123** as a yellow oil, which solidified over on standing overnight (2.55 g, 98%); mp 94 – 96 °C (from toluene); (Found C, 68.8; H, 7.45; N, 5.45; $C_{15}H_{19}NO_3$ requires C, 68.95; H, 7.3; N, 5.35%); δ_H 10.66 (1H, s, br), 7.12 (1H, t, 3J 8.6), 6.68 – 6.50 (3H, m), 4.18 (2H, q, 3J 6.9), 2.40 – 2.31 (4H, m), 1.68 – 1.52 (4H, m) and 1.31 (3H, t, 3J 6.9); δ_C 171.08 (quat), 157.09 (quat), 156.48 (quat), 140.58 (quat), 129.50, 116.89, 111.64, 111.51, 92.70 (quat), 59.34 (CH_2), 28.07 (CH_2), 23.55 (CH_2), 22.44 (CH_2), 22.06 (CH_2) and 14.31 (CH_3); m/z 261 (M^+ , 40%), 187 (100), 170 (42), 142 (39) and 124 (63).

6-Hydroxy-7,8,9,10-tetrahydropyrido[1,2-*a*]quinolin-1-one **4.125**



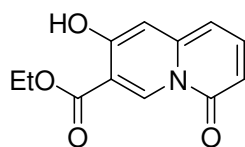
Pyrolysis of compound **4.123** (w 0.5786 g, T_f 500 °C, T_i 170 °C, P $2.6 - 2.9 \times 10^{-2}$ Torr, t 1 h) gave a yellow solid which was heated in methanol to remove any residual starting material. Filtration gave 6-hydroxy-7,8,9,10-tetrahydro-pyrido[1,2-*a*]quinolin-1-one **4.125** as a yellow solid (0.2433 g, 51%); mp 227 – 229 °C; [Found (M+H)⁺ 216.10137, C₁₃H₁₄NO₂ requires 216.10191]; δ_H (*d*₆-DMSO, 360 MHz) 11.62 (1H, s), 7.33 (1H, t, ³*J* 7.9), 6.76 (1H, s), 6.23 (1H, d, ³*J* 7.3), 3.32 – 3.28 (2H, m), 2.59 – 2.58 (2H, m) and 1.77 – 1.61 (4H, m); δ_C (*d*₆-DMSO, 90 MHz) 161.58 (quat), 156.71 (quat), 145.94 (quat), 142.55 (quat), 136.74, 119.80, 105.30, 101.08, 98.91, 30.17 (CH₂), 22.52 (CH₂), 22.28 (CH₂) and 20.45 (CH₂); *m/z* (+ve ESI) 216 [(M+H)⁺, 100%]

Diethyl 2-[(3-hydroxyphenylamino)methylene]malonate **4.126**



Using general method B, 3-aminophenol (1.09 g, 10 mmol) gave diethyl 2-[(3-hydroxyphenylamino)methylene]malonate **4.126** (2.75 g, quant.); mp 150 – 151 °C (from ethanol, lit.,¹¹³ 155 °C); δ_H 10.95 (1H, d, ³*J* 13.6), 8.51 (1H, d, ³*J* 13.6), 7.24 (1H, t, ³*J* 8.0), 6.71 – 6.65 (3H, m), 6.32 (1H, s br), 4.25 (4H, m) and 1.34 (6H, m); δ_C 169.91 (quat), 166.26 (quat), 157.39 (quat), 151.98, 140.49 (quat), 130.80, 112.18, 109.53, 104.71, 93.97 (quat), 60.48 (CH₂), 60.37 (CH₂), 14.38 (CH₃) and 14.26 (CH₃).

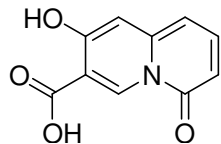
7-Carbethoxy-8-hydroxyquinolizin-4-one **4.127**



Pyrolysis of compound **4.126** (w 5.384 g, T_f 500 °C, T_i 180 °C, P $1.6 - 2.9 \times 10^{-2}$ Torr, t 2.5 h) gave 7-carbethoxy-8-hydroxyquinolizin-4-one **4.127** as a yellow solid (4.031 g, 90%); mp 129-130 °C (from ethanol); (Found C, 62.15; H, 4.7; N, 5.95. C₁₂H₁₁NO₄ requires C, 61.8; H, 4.7; N 6.0%); δ_H 10.69 (1H, s, br), 9.62 (1H, s), 7.56 (1H, dd, ³*J* 8.8, ⁴*J* 7.8), 6.80 (1H, s), 6.38 (1H, d, ³*J* 7.8), 6.30 (1H, dd, ³*J* 8.8, ⁴*J* 1.1), 4.48 (2H, q, ³*J* 7.1) and 1.45 (3H, t, ³*J* 7.1); δ_C 168.43 (quat), 158.85 (quat), 157.57 (quat), 146.18 (quat), 140.96, 135.38, 108.94 (quat), 106.08, 105.20, 100.82, 63.29 (CH₂) and 14.58

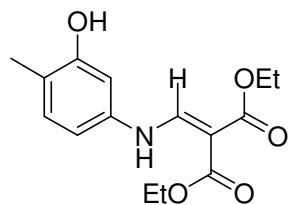
(CH₃); m/z 233 (M⁺, 58%), 187 (100), 159 (52), 131 (29) and 103 (29).

7-Carboxy-8-hydroxyquinolizin-4-one **4.128**



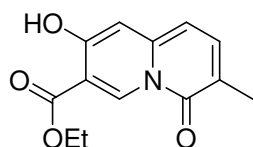
To a stirred solution of 7-carboethoxy-8-hydroxyquinolizin-4-one **4.127** (0.466 g, 2 mmol) in THF (20 cm³), MeOH (20 cm³) and water (10 cm³), was added lithium hydroxide hydrate (1.06 g) and the mixture stirred overnight at room temperature. The mixture was added to water (100 cm³) and acidified with HCl (2M). A yellow precipitate was filtered off (0.2139 g), the aqueous layer was extracted with ethyl acetate (3 × 20cm³), dried over MgSO₄ and the solvent removed to give a second crop of product (0.1175 g, total yield 0.331 g, 81%); mp 246 – 247 °C (decomp.); [Found (M+H)⁺ 206.04524, C₁₀H₈NO₄ requires 206.04478]; δ_H (*d*₆-DMSO) 9.22 (1H, s), 7.35 (1H, t, ³*J* 8.2), 6.77 (1H, s), 6.27 (1H, d, ³*J* 7.8) and 5.87 (1H, d, ³*J* 8.5); δ_C (*d*₆-DMSO) 168.20 (quat), 158.27 (quat), 146.10 (quat), 133.73, 111.71 (quat), 105.47, 102.84 and 100.16; m/z (+ve ESI) 206 [(M+H)⁺, 11%].

Diethyl 2-[(3-hydroxy-4-methylphenylamino)methylene]malonate **4.129**



Using general method B, 4-amino-*o*-cresol (0.615 g, 5 mmol) gave diethyl 2-[(3-hydroxy-4-methylphenylamino)methylene] malonate **4.129** (1.49 g, quant.); mp 152 – 154 °C (from ethanol) (Found C, 61.55; H, 6.6; N, 4.75. C₁₅H₁₉NO₅ requires C, 61.45; H, 6.5; N 4.8%); δ_H 10.83 (1H, d, ³*J* 13.7), 8.40 (1H, d, ³*J* 13.7), 6.99 (1H, d, ³*J* 8.1), 6.59 (1H, d, ⁴*J* 2.2), 6.50 (1H, dd, ³*J* 8.1, ⁴*J* 2.2), 4.25 (4H, m), 2.14 (3H, s) and 1.34 (6H, m); δ_C 169.42 (quat), 167.03 (quat), 155.91 (quat), 152.73, 138.51 (quat), 132.19, 121.77 (quat), 109.55, 104.55, 93.00 (quat), 60.82 (2CH₂), 15.78 (CH₃), 14.76 (CH₃) and 14.64 (CH₃); m/z 293 (M⁺, 39%), 247 (12), 201 (100), 174 (11) and 123 (12).

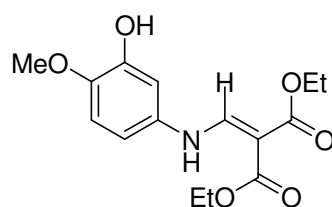
7-Carboethoxy-3-methyl-8-hydroxyquinolizin-4-one **4.132**



Pyrolysis of compound **4.129** (w 606 mg, *T_f* 500 °C, *T_i* 160 °C, *P*

2.6×10^{-2} Torr, t 30 min) gave 7-carbethoxy-3-methyl-8-hydroxyquinolizin-4-one **4.132** as an orange solid (0.425 g, 83%); mp 147-149 °C (from ethanol); (Found C, 63.15; H, 5.25; N, 5.65. $C_{13}H_{13}NO_4$ requires C, 62.7; H, 5.3; N 5.6%); δ_H (360 MHz) 9.79 (1H, s), 7.49 (1H, d, 3J 7.8), 6.74 (1H, s), 6.30 (1H, d, 3J 8.3), 4.43 (2H, q, 3J 7.1), 3.81 (3H, s) and 1.40 (3H, t, 3J 7.1); δ_C 167.90 (quat), 158.31 (quat), 155.31 (quat), 143.16 (quat), 139.54, 134.38, 114.50 (quat), 108.37 (quat), 105.10, 99.72, 62.58 (CH₂), 16.92 (CH₃) and 13.94 (CH₃); m/z 263 (M^+ , 70%), 217 (55), 174 (100), 171 (86), 143 (52) and 115 (86).

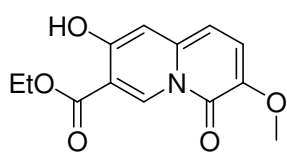
Diethyl 2-[(3-hydroxy-4-methoxyphenylamino)methylene]malonate **4.130**



Using general method B, 5-amino-2-methoxyphenol (0.378 g, 2.5 mmol) gave compound **4.130** (0.672 g, 87%); mp 88 – 91 °C (from acetonitrile); (Found C, 58.6; H, 5.9; N, 4.6. $C_{15}H_{19}NO_6$ requires C, 58.25; H, 6.15; N 4.55%);

δ_H 11.14 (1H, d, 3J 13.8), 8.64 (1H, d, 3J 13.8), 7.05 – 7.00 (2H, m), 6.81 (1H, dd, 3J 8.6, 4J 2.7), 4.56 – 4.46 (4H, m), 4.09 (3H, s) and 1.61 -1.50 (6H, m); δ_C 169.55 (quat), 166.34 (quat), 152.83, 147.26 (quat), 144.83 (quat), 133.84 (quat), 111.18, 109.37, 104.86, 92.88 (quat), 60.67 (CH₂), 60.40 (CH₂), 56.47 (CH₃), 14.80 (CH₃) and 14.68 (CH₃); m/z 309 (M^+ , 100%), 264 (64), 217 (17) and 174 (16).

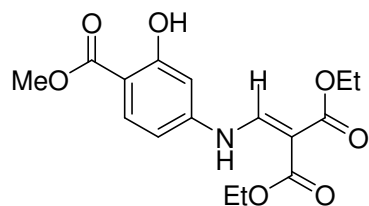
7-Carbethoxy-3-methoxy-8-hydroxyquinolizin-4-one **4.133**



Pyrolysis of compound **4.130** (w 242 mg, T_f 450 °C, T_i 120 °C, P $1.6 - 3.2 \times 10^{-2}$ Torr, t 30 min) gave 7-carbethoxy-3-methoxy-8-hydroxyquinolizin-4-one **4.133** as a red solid (159

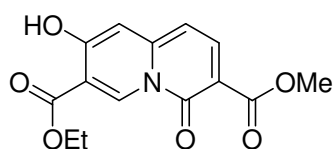
mg, 92%); mp 154-155 °C (from ethanol); (Found C, 59.15; H, 4.85; N, 5.25. $C_{13}H_{13}NO_5$ requires C, 59.3; H, 4.95; N 5.3%); δ_H 10.27 (1H, s, br), 9.66 (1H, s), 7.19 (1H, d, 3J 8.6), 6.66 (1H, s), 6.26 (1H, d, 3J 8.3), 4.43 (2H, q, 3J 7.1), 3.81 (3H, s) and 1.40 (3H, t, 3J 7.1); δ_C 168.44 (quat), 154.33 (quat), 153.86 (quat), 140.85 (quat), 138.86 (quat), 134.38, 121.03, 109.19 (quat), 105.38, 98.48, 63.14 (CH₂), 57.38 (CH₃), 14.58 (CH₃); m/z 263 (M^+ , 70%), 217 (55), 174 (100), 171 (86), 143 (52) and 115 (86).

Diethyl 2-[(3-hydroxy-4-carbomethoxyphenylamino)methylene]malonate **4.131**



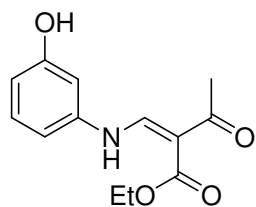
Using general method B, methyl 4-aminosalicylate (1.67 g, 10 mmol) gave compound **4.131** (3.72 g, 97%) as a mixture of isomers due to restricted rotation; mp 110 – 113 °C (from ethanol); (Found C, 56.40; H, 5.65; N, 4.10. C₁₆H₁₉NO₇ requires C, 56.65; H, 5.45; N, 3.9%); δ_H 10.95 – 10.87 (2H, m), 8.43 (1H, d, 3J 13.4), 7.87 (1H, d, 3J 8.6), 7.54 (1H, d, 3J 9.6), 6.65 (1H, d, 3J 2.2), 6.56 (1H, dd, 3J 8.7, 4J 2.3), 6.10 (1H, m), 4.31 – 4.10 (4H, m), 3.89 (3H, s), 3.82 (3H, s) and 1.36 – 1.21 (6H, m)

7-Carbethoxy-3-carbomethoxy-8-hydroxyquinolizin-4-one **4.134**



Pyrolysis of compound **4.131** (w 0.500 mg, T_f 500 °C, T_i 130 °C, P 3.2×10^{-2} Torr, t 30 min) gave 7-carbethoxy-3-carbomethoxy-8-hydroxyquinolizin-4-one **4.134** as an orange solid (0.383 g, 89%); mp 226 - 228 °C (from ethanol); (Found C, 57.75; H, 4.45; N, 4.8. C₁₄H₁₃NO₆ requires C, 58.0; H, 4.3; N 4.55%); δ_H 11.19 (1H, s, br), 10.00 (1H, s), 8.32 (1H, d, 3J 8.7), 6.93 (1H, s), 6.35 (1H, d, 3J 8.4), 4.52 (2H, q, 3J 7.2), 3.92 (3H, s) and 1.47 (3H, t, 3J 7.2); δ_C 168.12 (quat), 167.09 (quat), 161.95 (quat), 155.92 (quat), 150.13 (quat), 143.51, 136.97, 109.36 (quat), 107.28, 102.97 (quat), 100.67, 63.66 (CH₂), 52.34 (CH₃) and 14.46 (CH₃); m/z 291 (M⁺, 92%), 245 (100), 217 (41) and 189 (18).

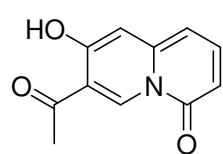
Ethyl 2-[1-(3-hydroxyphenylamino)-methylidene]-3-oxo-butyrate **4.136**



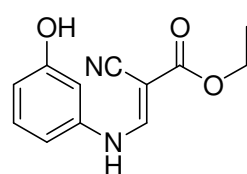
Ethyl 2-[1-ethoxymethylidene]-3-oxobutyrate (1.86 g, 10 mmol) was added to solution of 3-aminophenol (1.09 g, 10 mmol) in acetonitrile and stirred overnight. The precipitate was filtered off to give the first crop of product (0.484 g, 20%) and the filtrates concentrated to give an orange solid, which upon recrystallisation gave a second crop as a pale-yellow solid (1.116 g, 25%); mp 115 – 117 °C (from ethanol); (Found C, 62.45; H, 6.00; N,

5.4; C₁₃H₁₅NO₄ requires C, 62.65; H, 6.05; N, 5.60.); δ_H 12.73 (1H, d, 3J 13.5), 8.64 (1H, d, 3J 8.4), 7.36 (1H, t, 3J 7.5), 6.87 – 6.82 (3H, m), 4.38 (2H, q, 3J 7.0), 2.69 (3H, s) and 1.46 (3H, t, 3J 7.3); δ_C 201.14 (quat), 167.16 (quat), 157.95 (quat), 152.61, 139.82 (quat), 131.01, 113.45, 108.76, 105.59, 102.46 (quat), 60.34 (CH₂), 30.78 (CH₃), and 14.42 (CH₃); m/z 249 (M⁺, 77%), 204 (17), 188 (35), 175 (100), 160 (42) and 133 (13).

7-Acetyl-8-hydroxyquinolizin-4-one **4.137**

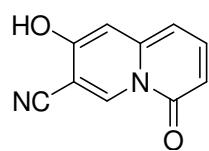
 Pyrolysis of compound **4.136** (w 0.2996 g, T_f 500 °C, T_i 160 °C, P $2.3 - 3.2 \times 10^{-2}$ Torr, t 40 min) gave 7-acetyl-8-hydroxyquinolizin-4-one **4.137** as a red solid (0.2289 g, 94%); mp 175 – 176 °C (from ethanol); (Found C, 65.0; H, 4.25; N, 6.8; C₁₁H₉NO₃ requires C, 65.0; H, 4.45; N, 6.9%); δ_H (360 MHz) 11.49 (1H, s, br), 9.81 (1H, s), 7.59 (1H, t, 3J 7.8), 6.78 (1H, s), 6.38 (1H, d, 3J 7.8), 6.35 (1H, dd, 3J 8.9, 4J 1.1) and 2.78 (3H, s); δ_C (360 MHz) 202.73 (quat), 158.27 (quat), 157.72 (quat), 145.39 (quat), 140.86, 136.03, 114.89 (quat), 105.85, 104.75, 100.31 and 26.36 (CH₃); m/z 203 (M⁺, 100%), 175 (45), 157 (48), 132 (12) and 104 (13).

Ethyl 2-cyano-3-(3-hydroxyphenylamino)acrylate **4.139**

 Ethyl ethoxymethylenecyanoacetate (2.7 cm³, 20 mmol) was added to a solution of 3-aminophenol (2.18 g, 20 mmol) dissolved in the minimum amount of acetonitrile. The solution was stirred for 3 h at room temperature and the white solid filtered off (1.47 g, 32%). Removal of the solvent from the filtrates gave a further portion of product (3.01 g, 65%). The product **4.139** was isolated as a 2:1 mixture of isomers. δ_H (*d*₆-DMSO) 10.88 (1H, m), 10.77 (1H, d, 3J 13.9), 9.83 (2H, m), 8.57 (1H, d, 3J 13.8), 8.36 (1H, m), 7.31 (1H, d, 3J 8.0), 7.28 (1H, d, 3J 7.9), 7.00 (1H, dd, 3J 7.9, 4J 1.8), 6.95 – 6.90 (3H, m), 6.75 – 6.69 (2H, m), 4.46 (2H, q, 3J 7.1), 4.30 (2H, q, 3J 7.1), 1.40 (3H, t, 3J 7.0) and 1.37 (3H, t, 3J 7.0); δ_C (*d*₆-DMSO) 166.37 (quat), 164.62 (quat), 158.38 (quat), 158.28 (quat), 153.30, 152.07, 140.77 (quat), 139.73 (quat), 130.33, 118.04 (quat), 115.082 (quat), 112.32, 112.07, 108.35, 108.27 (quat), 104.92, 74.21 (quat),

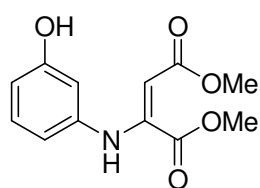
73.28 (quat), 60.42 (CH₂), 60.30 (CH₂), 14.27 (CH₃) and 14.17 (CH₃); 2 carbons not apparent.; m/z 232 (M⁺, 100), 187 (10), 158 (87) and 109 (8).

7-Cyano-8-hydroxyquinolizin-4-one **4.140**



Flash vacuum pyrolysis of compound **4.139** (w 0.505 g, T_f 600 °C, T_i 180 °C, P $2.1 - 2.7 \times 10^{-2}$ Torr, t 45 min.) gave 7-cyano-8-hydroxyquinolizin-4-one **4.140** as a yellow solid (0.325 g, 80%); mp 252 – 255 °C (decomp.); [Found (M+NH₄)⁺ 204.07707, C₁₀H₁₀N₃O₂ requires 204.07675] δ_H (360 MHz, d_6 -DMSO) 9.43 (1H, s), 7.69 (1H, t, 3J 8.8), 6.96 (1H, s), 6.61 (1H, d, 3J 7.8) and 6.22 (1H, dd, 3J 8.8, 4J 1.1); δ_C (90 MHz, d_6 -DMSO) 156.75 (quat), 155.57 (quat), 144.86 (quat), 140.83, 137.18, 114.02 (quat), 103.98, 103.80, 100.10 and 97.40 (quat); m/z (-ve ESI) 185 [(M-H)⁻, 100%].

Dimethyl (*E*)-2-(3-hydroxyphenylamino)-but-2-enedioate¹¹⁴ **4.141**

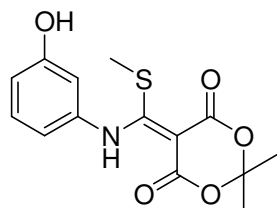


Dimethyl acetylenedicarboxylate (0.71 g, 5 mmol) was added to a solution of 3-aminophenol (0.545 g, 5 mmol) in methanol (5 ml) and the mixture stirred for 3 h. The solvent was removed and the resulting orange oil purified by column chromatography to give a yellow oil, which crystallised after time in the freezer (1.02 g, 82%); mp 89 – 91 °C ; δ_H 9.53 (1H, s), 7.10 (1H, t, 3J 8.0), 6.56 (1H, ddd, 3J 8.1, 4J 2.5, 5J 0.5), 6.17 (1H, s), 5.58 (1H, s), 3.80 (3H, s) and 3.78 (3H, s); δ_C 169.86 (quat), 165.00 (quat), 156.62 (quat), 147.83 (quat), 141.30 (quat), 129.96, 112.67, 111.44, 107.77, 93.62, 52.84 (CH₃) and 51.22 (CH₃).

Pyrolysis of Dimethyl (*E*)-2-(3-hydroxyphenylamino)-but-2-enedioate **4.141**

Pyrolysis of compound **4.141** gave a brown solid, the ¹H NMR spectrum of which did not indicate the presence of any identifiable products.

5-[(3-Hydroxyphenylamino)-methylsulfanylmethylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **4.142**



3-Aminophenol (0.55 g, 5 mmol) was dissolved in acetonitrile (20 cm³, 5 mmol) and 5-(bis-methylsulfanyl-methylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.24 g, 5 mmol) was added.

The mixture was allowed to stand for 15 min. and the solvent removed to give a yellow solid. Recrystallisation of the solid from ethanol gave 5-[(3-hydroxyphenylamino)-methylsulfanylmethylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **4.142** as a off-white solid (0.96 g, 62%); mp 142 – 145 °C (from ethanol); (Found M^+ 309.06700, C₁₄H₁₅NO₅S requires 309.06654); δ_H 7.75 (1H, br, s), 7.20 (1H, t, 3J 4.0), 6.90 (1H, t, 3J 2.2), 6.81 (1H, dd, 3J 9.0, 4J 0.8), 6.74 (1H, dd, 3J 8.0, 4J 1.3), 2.23 (3H, s) and 1.69 (6H, s); δ_C 178.83 (quat), 164.91 (quat), 158.07 (quat), 138.27, 130.91, 116.81, 116.07, 112.69, 103.92 (quat), 86.50 (quat), 26.72 (2CH₃) and 19.43 (CH₃); one quat not apparent.; m/z 309 (M^+ , 1%) and 207 (M-CO₂, Acetone, 100%).

Pyrolysis of 5-[(3-Hydroxyphenylamino)-methylsulfanyl-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione **4.142**

Pyrolysis of compound 4.142 (w 0.044 g, T_f 500 °C, T_i 200 °C, P 2.6 – 2.9 × 10⁻² Torr, t 13 min.) gave a yellow solid, which was dissolved in *d*₆-DMSO and the ¹H NMR spectrum recorded. The ¹H NMR spectrum showed a mixture of two products (7-hydroxy-2-methylsulfanyl-1*H*-quinolin-4-one **4.145** and 5-hydroxy-2-methylsulfanyl-1*H*-quinolin-4-one **4.144** in a 1:4 ratio.

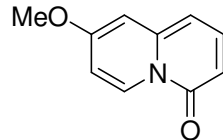
5-Hydroxy-2-methylsulfanyl-1*H*-quinolin-4-one **4.144**: δ_H (*d*₆-DMSO, 500 MHz) 7.49 (1H, t, 3J 8.2), 6.91 (1H, d, 3J 8.3), 6.57 (1H, d, 3J 8.0), 6.01 (1H, s) and 2.66 (3H, s)

7-Hydroxy-2-methylsulfanyl-1*H*-quinolin-4-one **4.145**: δ_H (*d*₆-DMSO, 500 MHz) 7.88 (1H, d, 3J 8.7), 6.82 (1H, s), 6.76 (1H, d, 3J 8.6), 5.87 (1H, s) and 2.59 (3H, s)

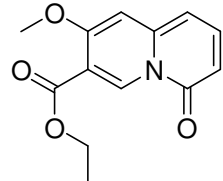
Reactions of Hydroxyquinolizin-4-ones

Reactions at Hydroxyl Group

8-Methoxyquinolizin-4-one **4.158**

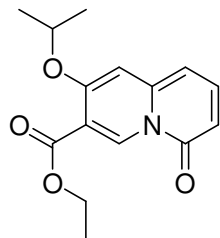
 A solution of 8-hydroxyquinolizinone (0.121 g, 0.75 mmol) in DMF (2.4 cm³) was added to sodium hydride (0.046 g, 1.9 mmol) and allowed to stir for 30 min. Iodomethane was added (0.2 cm³, 3.2 mmol) and the mixture was allowed to stir overnight. The mixture was added to water and extracted with ethyl acetate (3 × 30 cm³). The combined organic layers were separated, washed with brine (50 cm³), water (3 × 30 cm³) and dried over MgSO₄. Removal of the solvent gave 8-methoxyquinolizinone **4.158** (0.120 g, 91%); mp 104 - 106 °C (from cyclohexane); (Found M⁺ 175.06243, C₁₀H₉NO₂ requires 175.06278); δ_H 8.98 (1H, d, ³J 7.9), 7.50 (1H, t ³J 8.8), 6.64 – 6.58 (2H, m), 6.38 (1H, d, ³J 7.7), 6.30 (1H, dd, ³J 8.8, ⁴J 1.2) and 3.84 (3H, s); δ_C 160.40 (quat), 159.07 (quat), 145.25 (quat), 139.15, 129.69, 110.67, 105.79, 101.53, 101.06 and 56.26 (CH₃); *m/z* 175 (M⁺, 100%), 147 (64), 132 (80) and 104 (63).

7-Carbethoxy-8-methoxyquinolizin-4-one **4.159**

 A solution of 7-carbethoxy-8-hydroxyquinolizin-4-one (0.466 g, 2 mmol) and potassium carbonate (0.5 g) in DMF (6 cm³) was allowed to stir for 10 min. Iodomethane was added (0.5 cm³) and the mixture was allowed to stir overnight. The mixture was added to water and extracted with ethyl acetate (3 × 30 cm³). The combined organic layers were separated, washed with brine (50 cm³), water (3 × 30 cm³) and dried over MgSO₄. Removal of the solvent gave 7-carbethoxy-8-methoxyquinolizin-4-one **4.159** (0.404 g, 82%) as a yellow solid; mp 74 – 76 °C (from hexane); (Found M⁺ 247.08384, C₁₃H₁₃NO₄ requires 247.08391); δ_H 9.50 (1H, s), 7.42 (1H, t, 3J 8.5), 6.60 (1H, s), 6.32 – 6.29 (2H, m), 4.30 (2H, q, 3J 7.1), 3.94 (3H, s) and 1.32 (3H, t, 3J 7.1); δ_C 162.41 (quat), 158.22 (quat), 157.49 (quat), 144.40 (quat), 139.86, 133.68, 113.96 (quat), 106.10, 101.02, 100.46, 61.44 (CH₂), 56.24 (CH₃) and 14.00 (CH₃); *m/z* 247

(M⁺, 100%), 219 (25), 191 (28), 176 (12), 161 (27) and 133 (16).

7-Carbethoxy-8-isopropoxyquinolizin-4-one **4.160**



A solution of 7-carbethoxy-8-hydroxyquinolizin-4-one (0.466 g, 2.5 mmol) and potassium carbonate (0.5 g) in DMF (10 cm³) was allowed to stir for 10 min. 2-Iodopropane was added (1 cm³) and the mixture was allowed to stir overnight. The mixture was added to water and extracted with ethyl acetate (3 × 50 cm³). The combined organic layers were separated, washed with brine (50 cm³), water (3 × 50 cm³) and dried over MgSO₄. Removal of the solvent gave 7-carbethoxy-8-isopropoxyquinolizin-4-one **4.160** (0.612 g, 89%) as a yellow solid; mp 81 – 83 °C; (Found M⁺ 275.11511, C₁₅H₁₇NO₄ requires 275.11521); δ_H 9.56 (1H, s), 7.53 (1H, dd, ³J 8.8, ⁴J 7.6), 6.62 (1H, s), 6.37 – 6.33 (2H, m), 4.67 (1H, pentet, ³J 6.0), 4.37 (2H, q, ³J 7.0) and 1.45 – 1.35 (9H, m); δ_C 162.88 (quat), 158.45 (quat), 156.06 (quat), 144.86 (quat), 139.86, 133.76, 115.41 (quat), 105.65, 102.28, 100.31, 72.03, 61.49 (CH₂), 21.46 (2CH₃) and 14.17 (CH₃); *m/z* 275 (M⁺, 20%), 233 (37), 187 (100), 159 (23), 131 (15) and 103 (11).

Attempted Allylation or Benzylation of Quinolizinones.

Using sodium hydride, potassium *tert*-butoxide or potassium carbonate as the base in conjunction with DMF as the solvent and allyl or benzyl bromide gave complex mixtures of products with both compounds **4.69** and **4.127**, inseparable by column chromatography. Similar results were obtained with refluxing acetone in place of DMF.

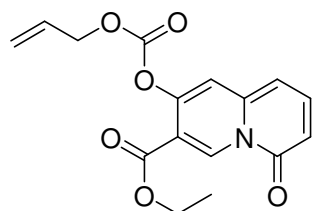
Attempts to apply Mitsunobu conditions⁹¹ (benzyl alcohol, PPh₃, DIAD) to benzylate compound **4.127** also yielded similar results.

Rearrangement of alloxycarbonyl precursor **4.165** (below), using Pd(PPh₃)₄ in THF⁹² to give the allyl compound was also attempted. Upon addition of the Pd, the solution turned red and upon work up gave a similar mixture of products to direct allylation.

General Method C – Acetylation Reactions

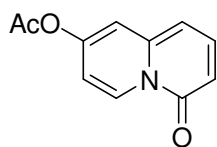
Triethylamine (0.22 cm³ per mmol) was added to a solution of compound **4.69** or **4.127** (1 equivalent) in DCM (*ca.* 10 cm³) and the resulting solution cooled to 0 °C. The acid chloride or chloroformate (1.5 equivalents) was added and the mixture stirred for 2 h at room temperature. The mixture was washed with NaOH (1 M, 25 cm³), brine (25 cm³), dried over MgSO₄ and the solvent removed to give the product

7-Carbethoxy-8-allyloxycarbonylquinolizin-4-one **4.165**



Using general method C, compound **4.127** (0.699 g, 3 mmol) and allyl chloroformate (0.38 cm³) gave 7-carbethoxy-8-allyloxycarbonylquinolizin-4-one **4.165** as a yellow solid (0.877 g, 92%); mp 83 – 85 °C (from cyclohexane); (Found M⁺ 317.08894; C₁₆H₁₅NO₆ requires 317.08936); δ_H 9.74 (1H, s), 7.60 (1H, dd, ³J 9.1, ⁴J 7.5), 7.10 (1H, s), 6.55 (1H, dd, ³J 9.1, ⁴J 1.1), 6.49 (1H, d, ³J 7.6), 5.89 (1H, m), 5.38 (1H, dd, ³J 17.2, ⁴J 1.3), 5.28 (1H, dd, ³J 10.4, ⁴J 1.2), 4.71 (2H, dt, ³J 5.9, ⁴J 1.2), 4.28 (2H, q, ³J 7.1) and 1.35 (3H, t, ³J 7.1); δ_C 179.10 (quat), 162.00 (quat), 158.39 (quat), 142.70 (quat), 139.93, 135.12, 130.55, 119.81, 117.93 (quat), 116.62, 113.74 (quat), 110.40, 102.78, 69.98 (CH₂), 61.80 (CH₂), 14.01 (CH₃); *m/z* 317 (M⁺, 19%), 273 (46), 187 (100) and 159 (20).

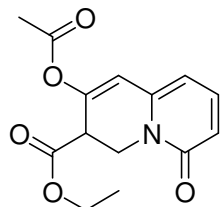
8-Acetoxyquinolizin-4-one **4.161**



8-Hydroxyquinolizinone (0.161 g, 1 mmol) was heated in acetic anhydride (5 cm³) until all the solid dissolved. The excess acetic anhydride was removed and the orange oil purified by Kugelrohr distillation to give 8-acetoxyquinolizinone **4.161** as a yellow oil (0.194 g, 94%); bp 78 °C (3.0 × 10⁻² Torr); (Found M⁺ 203.05718, C₁₁H₉NO₃ requires 203.05769) δ_H 9.07 (1H, d, ³J 8.0), 7.58 (1H, dd, ³J 8.8, ⁴J 7.7), 7.03 (1H, d, ³J 2.8), 6.80 (1H, dd, ³J 8.0, ⁴J 2.5), 6.57 (2H, m) and 2.31 (3H, s); δ_C 174.06 (quat), 158.86 (quat), 150.72 (quat), 143.14 (quat), 139.74, 129.27, 114.38, 111.90, 108.22, 103.62 and 21.06

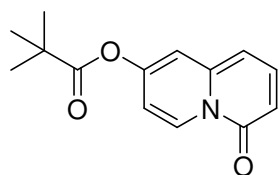
(CH₃); *m/z* 203 (M⁺, 20%), 174 (47), 161 (63), 151 (25), 133 (100) and 109 (51).

7-Carbethoxy-8-acetoxyquinolizin-4-one **4.162**



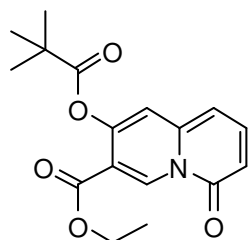
Using general method C, compound **4.127** (0.699 g, 3 mmol) and acetyl chloride (0.25 cm³) gave 7-carbethoxy-8-acetoxyquinolizin-4-one **4.162** as a yellow solid (0.8005 g, 95%); mp 110 – 111 °C (from cyclohexane); (Found M⁺ 275.07861, C₁₄H₁₃NO₅ requires 275.07882); δ_H 9.73 (1H, s), 7.63 (1H, dd, ³*J* 9.0, ⁴*J* 7.5), 7.06 (1H, s), 6.58 (1H, d, ³*J* 9.0), 6.52 (1H, d, ³*J* 7.2), 4.34 (2H, q, ³*J* 7.1), 2.36 (3H, s) and 1.37 (3H, t, ³*J* 7.1); δ_C 168.92 (quat), 162.02 (quat), 158.36 (quat), 148.72 (quat), 142.96 (quat), 139.93, 134.94, 116.98, 113.93 (quat), 110.04, 102.53, 61.70 (CH₂), 20.79 (CH₃) and 14.15 (CH₃); *m/z* 275 (M⁺, 12%), 233 (71), 187 (100), 159 (28), 131 (11) and 103 (10).

8-Trimethylacetoxiquinolizin-4-one **4.163**



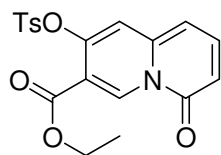
Using general method C, compound **4.69** (0.322 g, 2 mmol) and trimethylacetyl chloride (0.2 cm³) gave a brown-yellow solid. Recrystallisation from hexane gave 8-trimethylacetoxiquinolizin-4-one **4.163** as a brown-yellow solid (0.264 g, 53%); mp 86 – 88 °C (from hexane); (Found M⁺ 245.10478, C₁₄H₁₅NO₃ requires 245.10464); δ_H 9.13 (1H, d, ³*J* 8.0), 7.62 (1H, dd, ³*J* 8.0, ⁴*J* 7.7), 7.28 (1H, d, ³*J* 2.5), 6.78 (1H, dd, ³*J* 8.8, ⁴*J* 2.5), 6.59 – 6.54 (2H, m) and 1.36 (9H, s); δ_C 175.72 (quat), 158.51 (quat), 151.28 (quat), 143.36 (quat), 138.67, 129.42, 114.34, 111.71, 108.35, 102.89, 39.41 (quat) and 26.95 (3CH₃); *m/z* 245 (M⁺, 52%), 161 (100), 133 (63) and 84 (31).

7-Carbethoxy-8-trimethylacetoxiquinolizin-4-one **4.164**



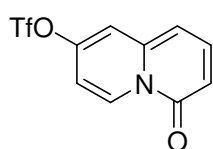
Using general method C, compound **4.127** (0.466 g, 2 mmol) and trimethylacetyl chloride (0.2 cm³) gave 7-carbethoxy-8-trimethylacetoxiquinolizin-4-one **4.164** as a brown-yellow solid (0.624 g, 99%); mp 90 – 91 °C (from cyclohexane); (Found M⁺ 317.12551; C₁₇H₁₉NO₅ requires 317.12577) δ_H 9.70 (1H, s), 7.64 (1H, dd, ³J 9.1, ⁴J 7.6), 7.06 (1H, s), 6.58 (1H, dd, ³J 9.1, ⁴J 1.2), 6.52 (1H, d, ³J 7.5), 4.34 (2H, q, ³J 7.0), 1.38 (9H, s) and 1.36 (3H, t, ³J 7.0); δ_C 176.15 (quat), 161.67 (quat), 158.27 (quat), 149.13 (quat), 142.87 (quat), 139.71, 134.25, 116.47, 114.58, 109.58, 102.30, 61.44 (CH₂), 39.01 (quat), 26.84 (3CH₃) and 14.00 (CH₃); *m/z* 317 (M⁺, 25%), 233 (100), 187 (87), 159 (13) and 115 (10)

7-Carbethoxy-8-(*p*-toluenesulfonyl)quinolizin-4-one **4.166**



p-Toluenesulfonyl chloride (0.400 g, 2.05 mmol) was added to a solution of 7-carbethoxy-8-hydroxyquinolizin-4-one (0.466 g, 2 mmol) and triethylamine (0.6 cm³) in CHCl₃ (10 cm³) and the resulting mixture stirred overnight. The solution was washed with HCl (2 M, 30 cm³), then brine (30 cm³), dried over MgSO₄ and the solvent removed to give 7-carbethoxy-8-(*p*-toluenesulfonyl)quinolizin-4-one **4.166** as a brown solid (0.7605 g, 98%); mp 172 -174 °C (from toluene); (Found C., 58.8; H., 4.45; N., 3.55; C₁₉H₁₇NO₆S requires C., 58.9; H., 4.4; N., 3.6%); δ_H 9.59 (1H, s), 7.84 (2H, d, ³J 6.6), 7.67 (1H, t, ³J 7.6), 7.37 (2H, d, ³J 6.6), 7.22 (1H, s), 6.62 (1H, d, ³J 7.6), 6.55 (1H, d ³J 7.6), 4.30 (2H, q, ³J 7.1), 2.55 (3H, s) and 1.42 (3H, t, ³J 7.1); δ_C 161.32 (quat), 158.12 (quat), 146.15 (quat), 146.09 (quat), 142.19 (quat), 139.86, 134.86, 131.90 (quat), 129.84 (2CH), 128.60 (2CH), 117.29, 114.83 (quat), 100.92, 103.23, 61.81 (CH₂), 21.65 (CH₃) and 13.97 (CH₃); *m/z* 387 (M⁺, 46%), 212 (34), 187 (73), 155 (58), 91 (83) and 86 (100).

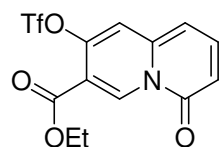
8-Trifluoromethylsulfonylquinolizin-4-one **4.167**



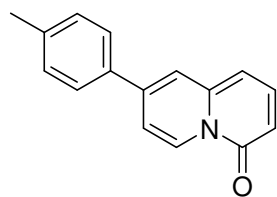
A suspension of 8-hydroxyquinolizinone (0.322 g, 2 mmol) in DCM (8 cm³) and triethylamine (0.6 cm³) was cooled to 0 °C and

trifluoromethanesulfonic anhydride (0.45 cm³) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 h. Water was added, the organic layer extracted and the aqueous layer washed with a further two portions of DCM. The organic layers were combined and washed with NaOH (20 cm³, 1 M), brine and water, dried over MgSO₄ and the solvent removed to give a dark brown oil. The crude product can be used in cross couplings or purified using column chromatography (EtOAc/Hexane, 2:3) to give 8-trifluoromethylsulfonylquinolizin-4-one **4.167** as a brown solid (0.281 g, 48%). mp 96 - 98 °C; (Found M⁺ 292.99744, C₁₀H₆F₃NO₄S requires 292.99641); δ_H (360 MHz) 9.13 (1H, d, ³J 8.0), 7.70 (1H, t, ³J 8.3), 7.34 (1H, d, ³J 2.6), 6.84 (1H, dd, ³J 8.1, ⁴J 2.7) and 6.67 (2H, d, ³J 8.4); δ_C (90 MHz) 158.09 (quat), 148.54 (quat), 141.73 (quat), 139.12, 130.87, 123.78 (CF₃), 120.23 (CF₃), 116.68 (CF₃), 115.76, 113.14 (CF₃), 111.15, 109.27 and 104.07; δ_F (235 MHz) -73.9; *m/z* 293 (60), 201 (7), 132 (67), 104 (30) and 73 (100).

7-Carbethoxy-8-trifluoromethylsulfonylquinolizin-4-one **4.174**

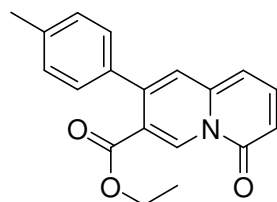
 A suspension of 7-carbethoxy-8-hydroxyquinolizin-4-one **4.127** (0.699 g, 3 mmol) in DCM (15 cm³) and triethylamine (0.9 cm³) was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.8 cm³) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 h. Water was added, the organic layer extracted and the aqueous layer washed with a further two portions of DCM. The organic layers were combined and washed with NaOH (20 cm³, 1 M), brine and water, dried over MgSO₄ and the solvent removed to give a dark brown oil. The product was purified using column chromatography (EtOAc/Hexane, 2:3) to give 7-carbethoxy-8-trifluoromethylsulfonylquinolizin-4-one **4.174** as a brown solid (0.6072 g, 55%); mp 111 – 113 °C; (Found M⁺ 365.01827, C₁₃H₁₀F₃NO₆S requires 365.01754) δ_H 9.65 (1H, s), 7.65 (1H, dd, ³J 9.2, ⁴J 7.5), 7.18 (1H, s), 6.64 (1H, dd, ³J 9.2, ⁴J 1.0), 6.59 (1H, d, ³J 7.5), 4.42 (2H, q, ³J 7.1) and 1.38 (3H, t, ³J 7.1); δ_C 161.13 (quat), 157.94 (quat), 145.99 (quat), 141.34 (quat), 140.15, 136.00, 117.48, 113.06 (quat), 112.51, 104.09, 32.43 (CH₂) and 13.97 (CH₃) (CF₃ not apparent); δ_F (235 MHz) -74.2; *m/z* 365 (M⁺, 100%), 245 (25), 204 (32) and 187 (38).

8-*p*-Tolylquinolizin-4-one **4.169**



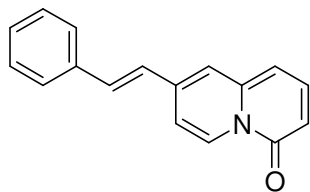
A suspension of compound **4.167** (0.147 g, 0.5 mmol), Pd(PPh₃)₄ (12 mg), K₂CO₃ (0.250 g), *p*-tolylboronic acid (0.068 g) in dioxane/water (6 cm³, 3:1 ratio) was heated at reflux for 14 h. The mixture was poured into water, extracted with ethyl acetate (3 × 30 cm³), dried over MgSO₄ and the solvent removed to give 8-*p*-tolylquinolizin-4-one **4.169** as an orange solid (0.0916 g, 78%); mp 136 – 139 °C; (Found M⁺ 235.09894, C₁₆H₁₃NO requires 235.09917); δ_H 9.17 (1H, d, ³*J* 7.6), 7.68 – 7.60 (4H, m), 7.37 – 7.28 (3H, m), 6.70 (1H, d, ³*J* 7.6), 6.60 (1H, dd, ³*J* 8.6, ⁴*J* 1.1) and 2.44 (3H, s); δ_C 158.54 (quat), 142.92 (quat), 141.39 (quat), 139.74, 133.28 (quat), 132.21 (quat), 129.97 (2CH), 127.60, 126.59 (2CH), 120.97, 114.51, 108.40, 103.63 and 21.27 (CH₃); *m/z* 235 (M⁺, 85%), 207 (100), 191 (5) and 103 (8).

7-Carbethoxy-8-*p*-tolylquinolizin-4-one **4.175**



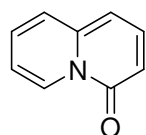
A suspension of compound **4.174** (0.183 g, 0.5 mmol), Pd(PPh₃)₄ (15 mg), Cs₂CO₃ (0.326 g), *p*-tolylboronic acid (0.068 g) in dioxane/water (6 cm³, 3:1 ratio) was heated at reflux for 14 h. The mixture was poured into water, extracted with ethyl acetate (3 × 30 cm³), dried over MgSO₄ and the solvent removed to give 7-carbethoxy-8-*p*-tolylquinolizin-4-one **4.175** as a yellow solid. The solid was purified by column chromatography (3:2 hexane/ethyl acetate) to give the product as a yellow solid (0.0536 g, 35%); mp 147 – 149 °C; (Found M⁺ 307.11995, C₁₉H₁₇NO₃ requires 307.12030); δ_H 9.62 (1H, s), 7.67 (1H, t, ³*J* 8.5), 7.33 (1H, s), 7.24 – 7.20 (4H, m), 6.62 (2H, d, ³*J* 8.5), 4.23 (2H, q, ³*J* 7.1), 2.40 (3H, s) and 1.21 (3H, t, ³*J* 7.1); δ_C 164.91 (quat), 158.40 (quat), 142.08 (quat), 141.84 (quat), 139.45, 138.48 (quat), 134.79 (quat), 131.47, 128.96 (2CH), 127.70 (2CH), 125.60, 119.99 (quat), 109.82, 103.12, 61.62 (CH₂), 21.26 (CH₃) and 13.92 (CH₃); *m/z* 307 (M⁺, 46%), 279 (15), 251 (24), 241 (100) and 139 (77).

8-Styrylquinolizin-4-one **4.176**



A suspension of compound **4.167** (0.293 g, 1 mmol), Pd(OAc)₂ (30 mg), NaOAc (0.300 g) and styrene (0.9 cm³) in NMP (6 cm³) was heated to 120 °C for 20 h.¹¹⁵ The mixture was poured into water (30 cm³) and extracted with ether (3 × 30 cm³). The organic layers were washed with NaOH (1 M) and water, dried over MgSO₄ and the solvent removed to give the crude product as a oil. The oil was purified by column chromatography to give 8-styryl-quinolizin-4-one **4.176** as a yellow solid (0.0922 g, 37%); mp 179 - 182 °C (from cyclohexane); (Found M⁺ 247.09999, C₁₇H₁₃NO requires 247.09917); δ_H (360 MHz) 9.06 (1H, d, ³J 7.7), 7.61 (1H, dd, ³J 8.6, ⁴J 7.6), 7.56 – 7.54 (2H, m), 7.43 – 7.38 (2H, m), 7.36 – 7.34 (2H, m), 7.28 (1H, d, ³J 16.2), 7.23 (1H, dd, ³J 7.9, ⁴J 2.2), 7.05 (1H, d, ³J 16.2), 6.62 (1H, d, ³J 7.9) and 6.56 (1H, dd, ³J 7.9, ⁴J 1.0); δ_C (90 MHz) 158.52 (quat), 142.59 (quat), 138.40, 137.90 (quat), 135.83 (quat), 133.53, 128.83, 128.76 (2CH), 127.08, 126.95 (2CH), 124.60, 122.79, 111.56, 108.98 and 103.60; *m/z* 247 (M⁺ 100%), 219 (85), 189 (7) and 129 (11).

Quinolizin-4-one **4.81**



Triethylsilane (0.2 cm³, 1.25 mmol) was added to a suspension of 8-trifluoromethylsulfonylquinolizin-4-one (0.147 g, 0.5 mmol), palladium acetate (2.5 mg) and dppp (4 mg) in DMF (2.5 cm³) and the reaction mixture stirred overnight. Wet ethyl acetate was added and the aqueous layer extracted with ethyl acetate (3 × 30 cm³). The combined organics were washed with Na₂CO₃, sat. NaCl, dried over MgSO₄ and the solvent removed to give a brown oil, purified by dry flash chromatography (hexane/ethyl acetate, 3:2) to remove the triethylsilanol produced in the reaction. The methanol washings from the column gave a second brown solid, identified as quinolizin-4-one **4.81** (0.035g, 48%). Yellow crystals were obtained by Kugelrohr distillation of the brown oil under vacuum.; bp 57 °C (3.4 × 10⁻² Torr); NMR data consistent with literature data.⁸⁵

Electrophilic Aromatic Substitution Reactions of 8-Hydroxyquinolizinones

Reaction with Deuteriated-TFA

The compound was dissolved in *d*-TFA and monitored over time by ^1H NMR spectroscopy at 360 MHz. The ratio of integrals was used to measure the reactivity of individual protons to deuterium exchange. The protons were assigned based on the change in chemical shift from their d_6 -DMSO ^1H NMR spectra.

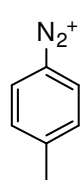
Compound	δ_{H1} DMSO	δ_{H1} TFA	δ_{H3} DMSO	δ_{H3} TFA
4.69	6.52	7.20	6.04	6.79
4.127	6.38	7.26	6.30	6.84

Table 4.13 Chemical shifts of the protons in the 1- (δ_{H1}) and 3- (δ_{H3})positions of 8-hydroxyquinolizinones **4.69** and **4.127** in d_6 -DMSO and TFA

8-Hydroxyquinolizinone **4.69** δ_H (TFA) 8.86 (1H, d, 3J 7.7), (1H, t, 3J 8.0), 7.27 – 7.19 (3H, m) and 6.79 (1H, d, 3J 8.0)

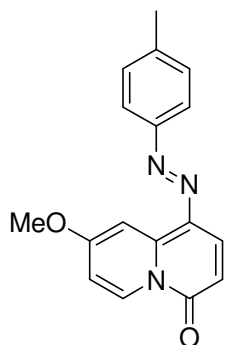
7-Carboethoxy-7-hydroxyquinolizinone **4.127** δ_H (TFA) 9.59 (1H, s), 7.71 (1H, m), 7.29 – 7.26 (2H, m), 6.84 (1H, d, 3J 7.9), 4.37 (2H, q, 3J 7.2) and 1.22 (3H, t, 3J 7.2)

p-Tolyldiazonium Tetrafluoroborate **4.177**



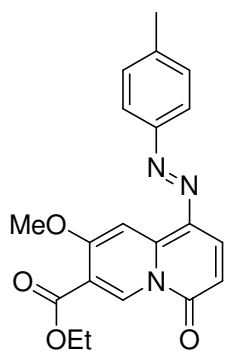
A solution of *p*-toluidine (5.35 g, 5 mmol) in fluoroboric acid (17 cm³) and water (20 cm³) was cooled to 0 °C and a solution of sodium nitrite (3.45 g) in water (7.5 cm³) was added. The mixture was stirred for 0.5 h and the precipitate filtered. The solid was dissolved in the minimal amount of acetone and reprecipitated using ether to give a white solid (9.54 g, 93%); mp 103 – 105 °C (lit.,¹¹⁶ 101 – 102 °C)

8-Methoxy-1-(*p*-tolylazo)quinolizin-4-one **4.178**



p-Tolyldiazonium tetrafluoroborate (0.103 g, 0.5 mmol) was added to a solution of 8-hydroxyquinolizin-4-one (0.081 g, 0.5 mmol) in DMF (5 cm³). The mixture was stirred for 30 min and then potassium carbonate (0.14 g) and methyl iodide (0.5 cm³) were added. The resulting solution was stirred overnight at room temperature. The mixture was diluted with water and extracted with ethyl acetate (3 × 30 cm³). The extracts were combined, washed with NaHCO₃ twice, brine, dried over MgSO₄ and the solvent removed to give 8-methoxy-1-(*p*-tolylazo)quinolizin-4-one **4.178** as a deep red solid (0.137 g, 93%); mp 161 – 163 °C (from toluene); (Found M⁺ 293.11575, C₁₇H₁₅N₃O₂ requires 293.11588); δ_H (360 MHz) 8.98 (1H, d, ³*J* 7.6), 8.29 (1H, d, ³*J* 9.7), 7.95 (1H, d, ³*J* 2.8), 7.68 (2H, d, ³*J* 8.3), 7.25 (2H, d, ³*J* 8.2), 6.75 (1H, dd, ³*J* 7.9, ⁴*J* 2.9), 6.38 (1H, d, ³*J* 9.7), 3.99 (3H, s) and 2.41 (3H, s); δ_C (90 MHz) 161.08 (quat), 158.48 (quat), 151.83 (quat), 145.58 (quat), 139.56 (quat), 129.56 (2CH), 129.52, 127.43 (quat), 127.03, 121.93 (2CH), 110.84, 106.19, 99.57, 56.00 (CH₃) and 21.32 (CH₃); *m/z* 293 (M⁺, 75%), 241 (29), 175 (45), 146 (100) and 91 (63). Trace amounts of a minor isomer could be observed in the ¹H NMR spectrum of the compound, but could not be isolated by column chromatography, with characteristic peaks at δ_H = 9.27, 7.87 and 6.27 ppm.

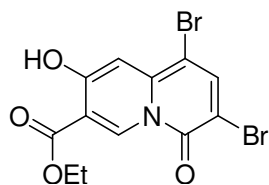
7-Carbethoxy-8-methoxy-1-(*p*-tolylazo)quinolizin-4-one **4.179**



p-Tolyldiazonium tetrafluoroborate (0.207 g, 1 mmol) was added to a solution of 7-carbethoxy-8-hydroxyquinolizin-4-one (0.233 g, 1 mmol) in DMF (5 cm³). The mixture was stirred for 30 min and then potassium carbonate (0.28 g) and methyl iodide (0.5 cm³) were added. The resulting solution was stirred overnight at room temperature. The mixture was diluted with water and extracted with ethyl acetate (3 × 30 cm³). The extracts were combined, washed with NaHCO₃ twice, brine, dried over MgSO₄ and the solvent removed to give 7-carbethoxy-8-methoxy-1-(*p*-tolylazo)quinolizin-4-one **4.179** as a deep red solid (0.325 g, 89%); mp 169 -171 °C (from toluene); (Found M⁺ 365.13694, C₂₀H₁₉N₃O₄

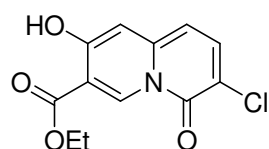
requires 365.13701); δ_H (360 MHz) 9.57 (1H, s), 8.37 (1H, d, 3J 9.7), 8.03 (1H, s), 7.69 (2H, d, 3J 8.3), 7.28 (2H, d, 3J 7.9), 6.44 (1H, d, 3J 9.7), 4.41 (2H, q, 3J 7.2), 4.11 (3H, s), 2.42 (3H, s) and 1.42 (3H, t, 3J 7.2); δ_C (90 MHz) 162.19 (quat), 158.81 (quat), 158.15 (quat), 150.88 (quat), 145.25 (quat), 140.00 (quat), 134.21, 129.61, 128.64 (2CH), 127.06 (quat), 121.98 (2CH), 114.70 (quat), 107.07, 97.12, 61.73 (CH₂), 56.59 (CH₃), 21.29 (CH₃) and 14.11 (CH₃); m/z 365 (M⁺, 100%) 254 (76), 218 (73), 129 (63), 91 (48). Trace amounts of a minor isomer could be observed in the ¹H NMR spectrum of the compound, but could not be isolated by column chromatography, with characteristic peaks at δ_H = 9.71, 8.59 and 6.61 ppm

1,3-Dibromo-7-carbethoxy-8-hydroxyquinolizin-4-one **4.180**



Bromine (5 drops) was added to solution of 7-carboethoxy-8-hydroxyquinolizin-4-one (0.233 g, 1 mmol) in CHCl₃ (5 cm³) and the resulting solution stirred for 15 min. The yellow precipitate was filtered to give 1,3-dibromo-7-carbethoxy-8-hydroxyquinolizin-4-one **4.180** (0.181 g). Concentration of the filtrates gave a second crop of product (0.163 g, total yield 0.318 g, 81%); mp 182 -185 °C (from ethanol); (Found C, 37.15; H, 1.95; N, 3.3. C₁₂H₉Br₂NO₄ requires C, 36.85; H, 2.3; N, 3.6 %); δ_H (360 MHz) 10.99 (1H, s), 9.89 (1H, s), 8.13 (1H, s), 7.31 (1H, s), 4.39 (2H, q, 3J 7.0) and 1.49 (3H, t, 3J 7.1); δ_C (90 MHz) 167.35 (quat), 159.35 (quat), 154.05 (quat), 144.97, 142.50 (quat), 136.06, 109.26 (quat), 106.57, 98.53 (quat), 90.00 (quat), 63.30 (CH₂) and 14.01 (CH₃); m/z 393 (M⁺, 27 %). 391 (M⁺, 43), 389 (M⁺, 21), 347 (51), 345 (100), 343 (52), 317 (20) and 289 (20)

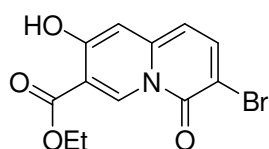
3-Chloro-7-carbethoxy-8-hydroxyquinolizin-4-one **4.182**



A solution of compound **4.127** (0.583 g, 2.5 mmol) in DCM (35 cm³) was cooled to -78 °C and stirred for 5 min. *N*-Chlorosuccinimide (0.347 g, 2.6 mmol) was added and the mixture stirred for 5 min, warmed to room temperature and stirred for a further 30 min. HCl (conc., 20 cm³) was added and the organic layer extracted with DCM (3 × 20 cm³). The combined organics were washed with water, dried over MgSO₄ and the

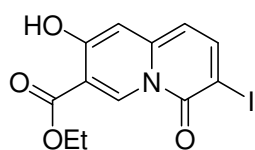
solvent removed to give a brown-orange solid. The solid was recrystallised from IPA to give 3-chloro-7-carboethoxy-8-hydroxyquinolizin-4-one **4.182** as an orange solid (0.397 g, 59%); mp 201 – 203 °C (from acetonitrile); [Found (M+H)⁺ 268.03727, C₁₂H₁₁³⁵ClNO₄ requires 268.03711]; δ_H 10.68 (1H, s), 9.79 (1H, s), 7.68 (1H, d, ³J 8.4), 6.86 (1H, s), 6.31 (1H, d, ³J 8.4), 4.46 (2H, q, ³J 7.1) and 1.40 (3H, t, ³J 7.1); δ_C 167.61 (quat), 157.18 (quat), 155.93 (quat), 144.36 (quat), 139.10, 134.84, 110.57, 109.10 (quat), 105.89, 99.57, 63.00 (CH₂) and 13.98 (CH₃); *m/z* (+ve ESI) 268 [(M+H)⁺, 100%] and 270 [(M+H)⁺, 29].

3-Bromo-7-carbethoxy-8-hydroxyquinolizin-4-one **4.181**



A solution of compound **4.127** (2.33 g, 10 mmol) in DCM (50 cm³) was cooled to -78 °C and stirred for 5 min. *N-N'*-Dibromo-5,5-dimethylhydantoin (2.89 g, 10.1 mmol) was added and the mixture stirred for 5 min, warmed to room temperature and stirred for a further 30 min. HCl (conc., 20 cm³) was added and the organic layer extracted with DCM (3 × 20 cm³). The combined organics were washed with water, dried over MgSO₄ and the solvent removed to give a brown-orange solid. The solid was recrystallised from ethanol to give 3-bromo-7-carbethoxy-8-hydroxyquinolizin-4-one **4.181** as an orange solid (1.791 g, 58%); mp 170 – 173 °C (from ethanol); (Found C., 45.6; H., 3.0; N., 4.5; C₁₂H₁₀BrNO₄·0.1H₂O requires C., 45.9; H., 3.2; N., 4.45%); δ_H 10.70 (1H, s), 9.79 (1H, s), 7.80 (1H, d, ³J 8.4), 6.78 (1H, s), 6.26 (1H, d, ³J 8.5), 4.31 (2H, q ³J 7.1) and 1.37 (3H, t, ³J 7.1); δ_C 167.58 (quat), 157.48 (quat), 145.06 (quat), 142.25, 135.15, 109.11 (quat), 105.97, 105.48 (quat), 100.33, 98.96 (quat), 62.99 (CH₂) and 13.96 (CH₃); *m/z* 313 (M⁺, 68%), 311 (M⁺, 68), 267 (100), 265 (100), 237 (20), 235 (20), 233 (15), 211 (10) and 209 (10).

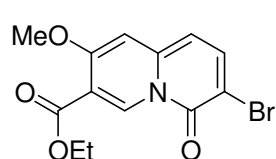
3-Iodo-7-carbethoxy-8-hydroxyquinolizin-4-one **4.183**



A solution of compound **4.127** (0.583 g, 2.5 mmol) in DCM (25 cm³) was cooled to -78 °C and stirred for 5 min. *N*-Iodosuccinimide (0.619 g, 2.75 mmol) was added and the

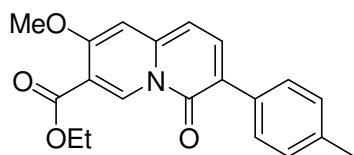
mixture stirred for 5 min, warmed to room temperature and stirred for a further 30 min. HCl (conc., 20 cm³) was added and the organic layer extracted with DCM (3 × 20 cm³). The combined organics were washed with water, dried over MgSO₄ and the solvent removed to give a brown-orange solid (0.780 g, quant.). The solid was recrystallised from IPA to give 3-iodo-7-carbethoxy-8-hydroxyquinolizin-4-one **4.183** as an orange solid (0.450 g, 50%); mp 138 – 140 °C (from ethanol); [Found (M+H)⁺ 359.97146, C₁₂H₁₁INO₄ requires 359.97273]; δ_H (500 MHz) 10.79 (1H, s), 9.86 (1H, s), 8.05 (1H, d, ³J 8.5), 6.84 (1H, s), 6.26 (1H, d, ³J 8.5), 4.51 (2H, q, ³J 7.0) and 1.47 (3H, t, ³J 7.0); δ_C 167.36 (quat), 157.57 (quat), 156.82 (quat), 154.93 (quat), 147.98, 145.72 (quat), 135.44, 108.90 (quat), 105.64, 101.67, 62.77 (CH₂) and 13.74 (CH₃); *m/z* (+ve ESI) 360 [(M+H)⁺, 24%].

3-Bromo-7-carbethoxy-8-methoxyquinolizin-4-one **4.184**



Dimethyl sulfate (1 cm³) was added dropwise to a stirred solution of compound **4.181** (1.560 g, 5 mmol) and K₂CO₃ (1.8 g) in acetone (40 cm³) and the mixture heated under reflux for 4 h. The mixture was cooled, the acetone removed under vacuum, the solid redissolved in ethyl acetate/water and the organic layer separated off. The aqueous layer was extracted with two further portions of ethyl acetate, the combined organic extracts washed NaOH (1 M), dried over MgSO₄ and the solvent removed under vacuum to give a gummy solid (1.768 g). Slurrying the solid in cyclohexane with a few drops of acetone, followed by filtration, gave 3-bromo-7-carbethoxy-8-methoxyquinolizin-4-one **4.184** as an orange solid (1.189 g, 73%); (Found M⁺ 324.99414, C₁₃H₁₂⁷⁹BrNO₄ requires 324.99442); δ_H (360 MHz) 9.54 (1H, s), 7.83 (1H, d, ³J 8.3), 6.68 (1H, s), 6.32 (1H, d, ³J 8.3), 4.38 (2H, q, ³J 7.1), 3.98 (3H, s) and 1.36 (3H, t, ³J 7.1); δ_C (90 MHz) 162.10 (quat), 157.81 (quat), 154.49 (quat), 143.84 (quat), 141.72, 133.94, 114.97 (quat), 101.31, 100.59, 100.45 (quat), 61.70 (CH₂), 56.47 (CH₃) and 13.97 (CH₃); *m/z* 327 (M⁺, 100%), 325 (M⁺, 100), 299 (24), 297 (24), 271 (24)m 269 (27) and 247 (76).

7-Carbethoxy-8-methoxy-3-*p*-tolylquinolizin-4-one **4.185**



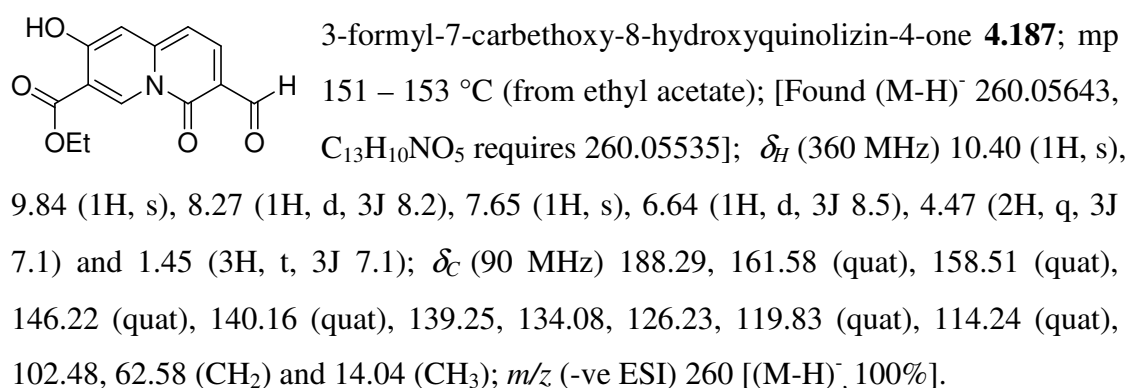
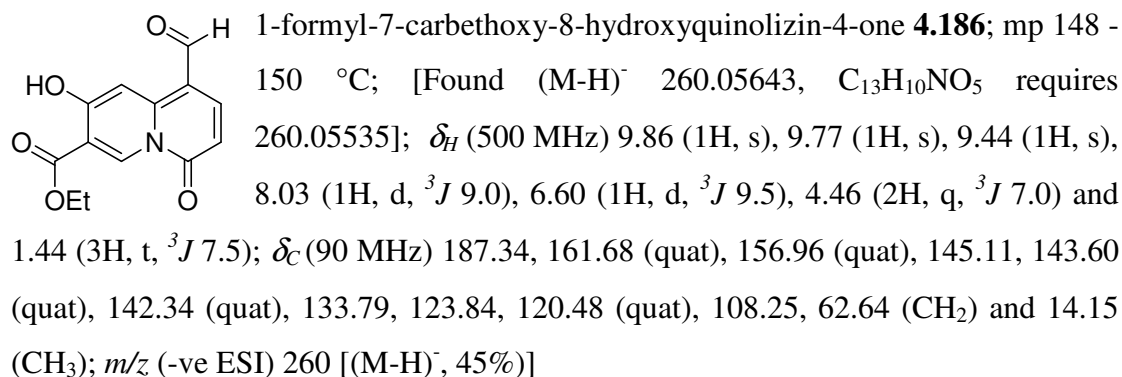
A solution of 3-bromo-7-carbethoxy-8-methoxyquinolizin-4-one **4.184** (0.163 g, 0.5 mmol), *p*-tolylboronic acid (0.069 g, 0.5 mmol), Pd(PPh₃)₄ (0.02 g) and K₂CO₃ (0.7 g) in dioxane/water (20 cm³, 3:1 mix) was heated to reflux for 4 h. The solution was cooled, the solvent removed and the residue was absorbed onto silica. Purification by dry flash column chromatography (3:2 ethyl acetate:hexane) gave 7-carbethoxy-8-methoxy-3-*p*-tolylquinolizin-4-one **4.185** as a yellow solid (0.0105 g, 6%); mp 180 – 183 °C; (Found M⁺ 337.13063, C₂₀H₁₉NO₄ requires 337.13086); δ_H (500 MHz) 9.75 (1H, s), 7.80 (1H, d, ³*J* 8.0), 7.70 (2H, d, ³*J* 8.0), 7.23 (2H, d, ³*J* 8.0), 6.67 (1H, s), 6.51 (1H, d, ³*J* 8.0), 4.38 (2H, q, ³*J* 7.0), 3.99 (3H, s), 2.38 (3H, s) and 1.39 (3H, t, ³*J* 7.0); δ_C (90 MHz) 162.67 (quat), 157.59 (quat), 143.50 (quat), 138.45, 137.04 (quat), 136.66 (quat), 134.64, 134.52 (quat), 128.94 (2CH), 128.24 (2CH), 117.20 (quat), 109.41 (quat), 101.21, 100.74, 61.65 (CH₂), 56.47 (CH₃), 21.20 (CH₃) and 14.20 (CH₃); *m/z* 337 (M⁺, 59%), 277 (68), 262 (100), 234 (26), 195 (26), 167 (24) and 149 (55).

Vilsmeier-Haack Formylation

DMF (1.25 cm³) was added with stirring to phosphoryl chloride (2.5 cm³), keeping the temperature between 10 – 20 °C. 1,2-Dichloroethane (10 cm³) was added and the solution cooled in ice to 0 – 5 °C. A solution of 7-carbethoxy-8-hydroxyquinolizin-4-one (1.165 g, 5 mmol) in 1,2-dichloroethane (20 cm³) was added dropwise over 10 min. The resulting mixture was heated to reflux for 15 min and then cooled to room temperature. The solution was cooled in an ice bath and a solution of sodium acetate (19 g) in water (25 cm³) was added dropwise. The organic layer was separated off and the aqueous portion extracted with dichloromethane (4 × 40 cm³). The combined extracts were dried over MgSO₄ and the solvent removed to give a yellow solid, a 30:70 mixture of 1-formyl-7-carbethoxy-8-hydroxyquinolizin-4-one **4.186** and 3-formyl-7-carbethoxy-8-hydroxyquinolizin-4-one **4.187** (1.2232 g, 94%).

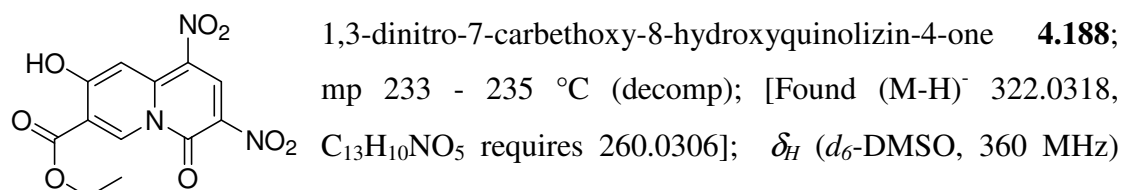
Recrystallisation from ethyl acetate yielded 3-formyl-7-carbethoxy-8-hydroxyquinolizin-4-one **4.187** as an orange solid (0.559 g, 43%). The residual material was then subjected to column chromatography to yield 1-formyl-7-

carbethoxy-8-hydroxyquinolizin-4-one **4.186** as a yellow solid (0.115 g, 9%).

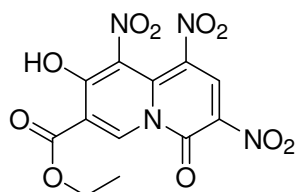


Nitration of 7-carbethoxy-8-hydroxyquinolizin-4-one

7-Carbethoxy-8-hydroxyquinolizin-4-one (0.699 g, 3 mmol) was dissolved in acetic acid (10 cm³) and nitric acid (conc., 1 cm³) was added. The resulting brown solution was stirred at room temperature for 1 h, added to ice-water, basified with sat. NaHCO₃ and reacidified with HCl (2 M). The solution was then extracted with ethyl acetate (5 × 100 cm³), washed with brine, dried over MgSO₄ and the solvent removed under vacuum to give a brown solid. The product was absorbed onto silica and purified by column chromatography (ethyl acetate) to give 1,3-dinitro-7-carbethoxy-8-hydroxyquinolizin-4-one **4.188** (0.242 g, 25%) and 1,3,9-trinitro-7-carbethoxy-8-hydroxyquinolizin-4-one **4.189** (0.370 g, 34%)



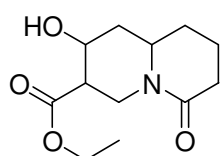
9.34 (1H, s), 9.24 (1H, s), 7.53 (1H, s), 4.32 (2H, q, 3J 7.1) and 1.35 (3H, t, 3J 7.1); δ_C (d_6 -DMSO, 90 MHz) 174.21 (quat), 164.25 (quat), 151.53 (quat), 138.97 (quat), 136.79, 134.06, 119.64 (quat), 119.23 (quat), 117.53 (quat), 111.90, 60.65 (CH₂) and 14.24 (CH₃); m/z (-ve, ESI) 322 [(M-H)⁻, 100%].



1,3,9-trinitro-7-carbethoxy-8-hydroxyquinolizin-4-one **4.189**;
mp 244 – 246 °C (decomp.); (Found M^+ 367.01528;
 $C_{12}H_7N_4O_{10}$ requires 367.01567) δ_H (d_6 -Acetone, 360 MHz)
9.73 (1H, s), 9.13 (1H, s), 4.46 (2H, q, 3J 7.1) and 1.40 (3H, t,
 3J 7.1); δ_C (d_6 -Acetone, 90 MHz) 169.20 (quat), 163.38 (quat), 149.21 (quat), 137.16
(quat), 137.05, 134.04, 133.78 (quat), 118.42 (quat), 117.43 (quat), 117.28 (quat),
61.11 (CH₂) and 12.74 (CH₃); m/z (-ve ESI) 367 [(M-H)⁻, 19%] and 321 (100).

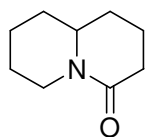
Hydrogenation Reactions

Hydrogenation of 7-carbethoxy-8-hydroxyquinolizin-4-one **4.127**



PtO₂ (0.08 g) was added to solution of compound **4.127** (0.466 g, 2 mmol) in ethanol (100 cm³). The flask was then evacuated and charged with nitrogen gas *via* balloon. The flask was evacuated again, charged with hydrogen gas *via* balloon and the mixture stirred overnight. The mixture was then filtered through a celite plug and the solvent removed under vacuum to give a pale yellow oil, the hydrogenated product as a mixture of 3 diastereomers in a 73:13:13 ratio by ¹H NMR spectroscopy. The solution was absorbed onto silica and purified by dry flash column chromatography to give the major diastereomer **4.190** as a colourless oil (0.0987 g, 20%), which solidifies upon storage in the freezer; mp 96 – 98 °C (Found M^+ 241.13088, $C_{12}H_{19}NO_4$ requires 241.13086); δ_H (360 MHz) 5.24 (1H, dd, 3J 13.9, 4J 2.5), 4.27 – 4.07 (3H, m), 3.82 (1H, m), 3.47 (1H, d, 3J 10.4), 3.27 (1H, m), 2.93 (1H, br, m), 2.56 (1H, dd, 3J 13.9, 4J 3.5), 2.39 – 2.22 (2H, m), 2.02 – 1.79 (3H, m), 1.71 – 1.49 (2H, m) and 1.24 (3H, t, 3J 7.1) δ_C (90 MHz) 172.48 (quat), 169.40 (quat), 68.89, 60.87 (CH₂), 54.86, 44.87, 42.40 (CH₂), 38.83 (CH₂), 32.74 (CH₂), 29.86 (CH₂), 19.13 (CH₂) and 13.90 (CH₃); m/z 241 (M^+ , 98%), 196 (40), 168 (100) and 150 (86).

Hydrogenation of 8-trimethylacetoxiquinolizinone **4.163**



PtO₂ (0.018 g) was added to solution of compound **4.163** (0.05 g, 0.2 mmol) in ethanol (20 cm³). The flask was then evacuated and charged with nitrogen gas *via* balloon. The flask was evacuated again, charged with hydrogen gas *via* balloon and the mixture stirred overnight. The mixture was then filtered through a celite plug and the solvent removed under vacuum to give a brown oil. Distillation of the brown oil gave octahydroquinolizin-4-one **4.191** as a clear oil (0.0089 g, 31%); bp 67 – 69 °C (1 Torr); δ_H 4.76 (1H, m), 3.21 (1H, m), 2.44 – 2.25 (3H, m), 2.01 – 1.90 (1H, m) and 1.88 – 1.33 (9H, m); δ_C (90 MHz) 169.42 (quat), 56.75, 42.33 (CH₂), 33.88 (CH₂), 32.77 (CH₂), 30.29 (CH₂), 25.20 (CH₂), 24.31 (CH₂) and 18.94 (CH₂). NMR spectrum matches literature data.¹⁰⁵

Hydrogenation of 7-carboethoxy-8-hydroxyquinolizin-4-one **4.127** – Catalyst/solvent screening

Catalyst Screening:

Catalyst (*ca.* 0.02 g) was added to solution of compound **4.127** (*ca.* 0.6 g, 0.25 mmol) in the ethanol (20 cm³). The flask was then evacuated and charged with nitrogen gas *via* balloon. The flask was evacuated again, charged with hydrogen gas *via* balloon and the mixture stirred overnight. The mixture was then filtered through a celite plug and the solvent removed under vacuum to give the crude material, which was dissolved in CDCl₃ and the ¹H NMR spectrum recorded. Ratios were measured based on integrals of the C6 equatorial hydrogen atom, which is observed at δ_H = 5.2 ppm in diastereomer 1, δ_H = 5.0 ppm in diastereomer 2 and δ_H = 4.8 in diastereomer 3.

Catalyst	%Diastereomer1	%Diastereomer2	%Diastereomer4	%Diastereomer4
PtO ₂ /C	73	13	13	0
Pd/C	44	39	17	0
Ru/C	No hydrogenation was observed.			
Rh/C	25	75	0	0
Rh/Al ₂ O ₃	As Rh/C, but with some partial hydrogenated products.			

Table 4.14 Diastereomeric ratios for the catalytic hydrogenation of compound **4.127** with various catalysts

Solvent screening:

PtO₂ (*ca.* 0.02 g) was added to solution of compound **4.127** (*ca.* 0.6 g, 0.25 mmol) in the reaction solvent (20 cm³). The flask was then evacuated and charged with nitrogen gas *via* balloon. The flask was evacuated again, charged with hydrogen gas *via* balloon and the mixture stirred overnight. The mixture was then filtered through a celite plug and the solvent removed under vacuum to give the crude material, which was dissolved in CDCl₃ and the ¹H NMR spectrum recorded.

Ethyl acetate gave comparable diastereoselectivity to ethanol in the hydrogenation reaction. DMF and a 9:1 mixture of ethanol and triethylamine gave only 7-carboethoxy-8-hydroxyquinolizin-4-one.

Chapter 5

Synthesis of

Pyrido[2,3-*d*]pyridazinediones

by Flash Vacuum Pyrolysis

5.1 Introduction

This work was performed in collaboration with P. Matyus of the Semmelweis University. The precursors were synthesised in Hungary and the pyrolysis experiments and calculations were performed by the author. The precursors were split into two types, based on their substitution pattern.

The first set of compounds (**5.1** – **5.3**) are based around a methylene Meldrum's acid derivative of 5-aminopyridazin-3-one ring system (Figure **5.1**).

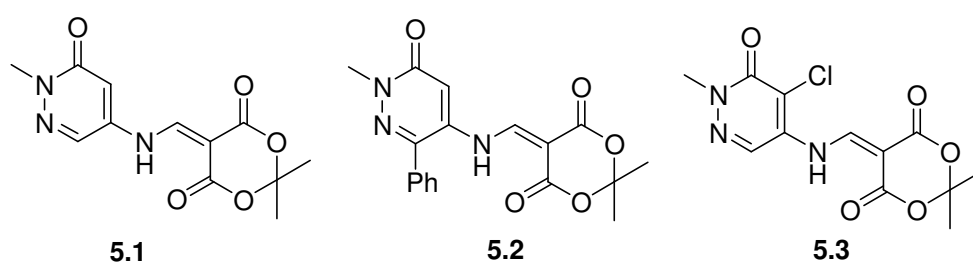
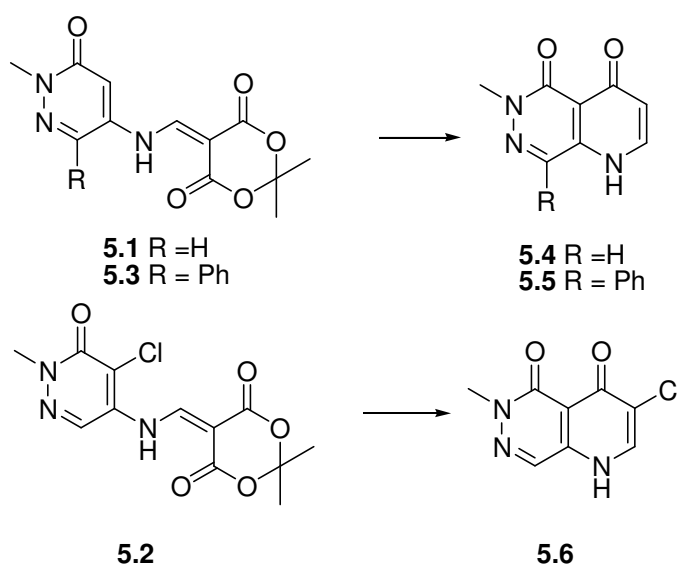


Figure 5.1 Structure of precursors **5.1** – **5.3**

It might be expected that pyrolysis of compounds **5.1** and **5.3** should give the fused pyridinone ring systems **5.4** and **5.5**. Based on the work in chapter 2, pyrolysis of the 2-chloro compound **5.2** might lead to the migration of the chlorine atom, giving compound **5.6** as the product (Scheme **5.1**).



Scheme 5.1 Proposed pyrolysis of compounds **5.1** – **5.3**

The second set of compounds are based around the corresponding Meldrum's acid derivative of 4-aminopyridazin-3-one ring system (Figure 5.2).

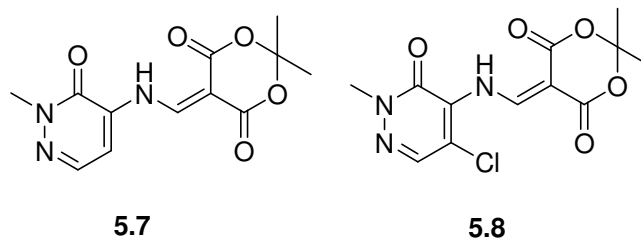
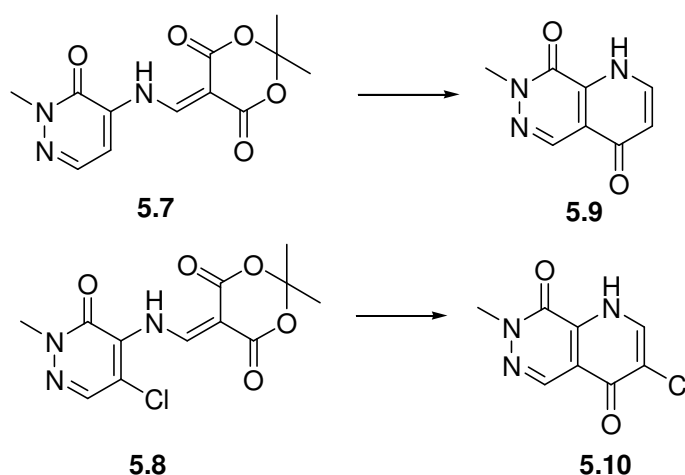


Figure 5.2 Structure of precursors **5.7** and **5.8**

Pyrolysis of compounds **5.7** and **5.8** should lead to the formation of fused compounds **5.9** and **5.10**, with the migration of the chlorine atom being expected with compound **5.10** (Scheme 5.2)



Scheme 5.2 Proposed pyrolysis of compounds **5.7** and **5.10**

Pyridopyridazines are known in the literature, but are generally heavily substituted.¹¹⁷ Pyridopyridazine-diones as shown above are unknown in the literature and may be of interest as a quinolinone-like structure.

5.2 Discussion

5.2.1. Pyrolysis of Compounds 5.1 – 5.3

Pyrolysis of compound **5.1** at 600 °C formed compound **5.4** an off-white solid. Acquiring NMR data of the compound proved problematic for a number of reasons. The compound is highly insoluble, even in DMSO. This problem is further complicated by broad peaks of the ^1H NMR spectrum (Figure 5.3).

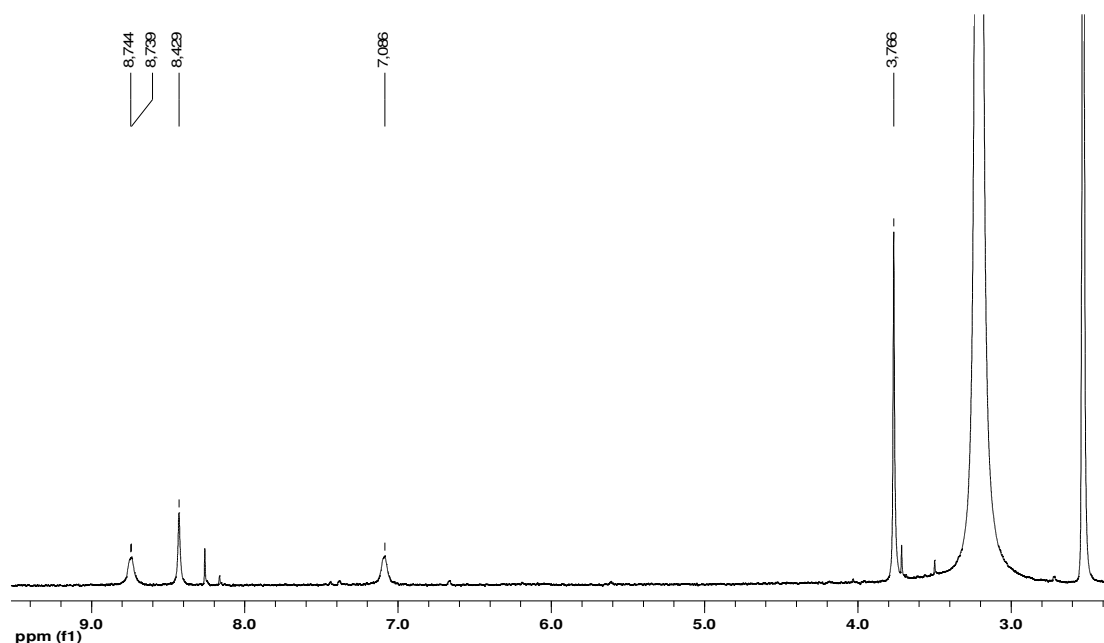
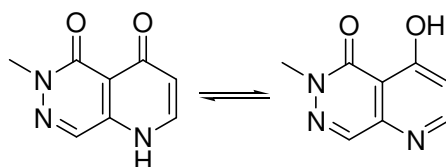


Figure 5.3 ^1H NMR spectrum (360 MHz) of compound **5.4**

The broadness of the peaks is indicative of an exchange process, most likely due to keto-enol tautomerisation of the pyridinone ring (Scheme 5.3)



Scheme 5.3 Tautomerism of compound **5.4**

In order to try to establish the tautomerism of the compound, a drop of TFA was

added to the DMSO solution. Without TFA, the tautomerisation is slow and occurring on the NMR time scale, leading to observed broad peaks. Upon addition of TFA, the tautomerisation is accelerated and gives an average spectrum. The result of this should be to sharpen the signals in the ^1H NMR spectrum of the compound (Figure 5.4)

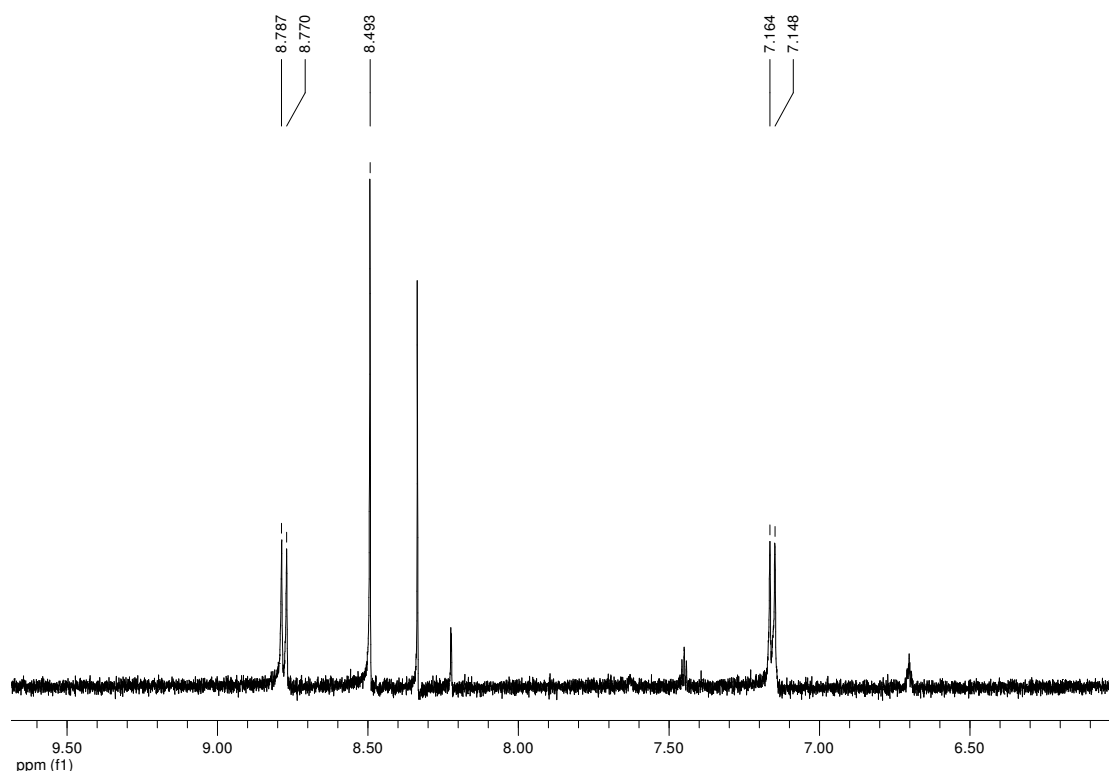
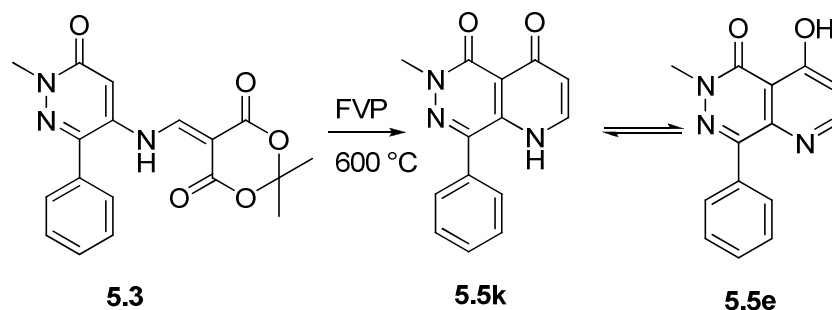


Figure 5.4 ^1H NMR spectrum (d_6 -DMSO/TFA, 360 MHz) of compound **5.4**

The ^1H NMR spectrum of compound **5.4** was sharpened upon addition of TFA to the DMSO solution, to give sharp doublets for the pyridone unit. The chemical shifts of the protons do not change significantly, so the compound has not been protonated by the TFA. The coupling constants for the doublets were found to be approximately 6 Hz. Using 4-methoxypyridine for comparison purposes, which has a coupling constant of 5.4 Hz,¹¹⁸ and quinolin-4-one, which has a coupling constant of 7.3 Hz, it can be said that the addition of TFA affects the rate of the equilibrium between the two tautomers, causing the average observed spectrum to be like that of the hydroxy tautomer.

Pyrolysis of the phenyl compound **5.3** at 600 °C led to the formation of a white solid,

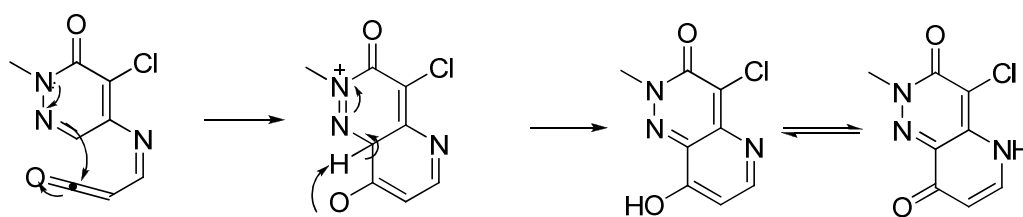
isolated in 96% yield. The molecular weight of the compound was found at $m/z = 253$, and the ^1H NMR spectrum of the compound showed only a single product with a spectrum consistent with compound **5.5** (Scheme 5.4)



Scheme 5.4 Pyrolysis of compound **5.3**

Unlike the unsubstituted system, the ^1H NMR spectrum of compound **5.3** showed no signs of broadness in the peaks. The coupling constants of compound **5.5**, which are 5.3 Hz, are more consistent with the enol- tautomer **5.5e** rather than the keto- tautomer **5.5k**. This based on comparisons with quinolin-4-one, which has a coupling constant of 7.3 Hz for the protons in the 2 and 3 positions,¹¹⁹ and 4-methoxypyridine, which has a coupling constant of 5.4 Hz for the equivalent protons.

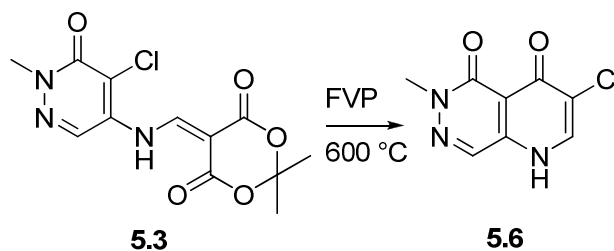
The chloro derivative **5.6** proved more insoluble in *d*₆-DMSO than compounds **5.4** and **5.5**, to the extent that no NMR data could be acquired. The high melting point is typical of molecules of this type. There are three possibilities for the product of these reaction. The first involves *ipso* attack of the imidoylketene and subsequent loss of the chlorine atom. This is unlikely to be the case, as the product would therefore be compound **5.4**, which has been characterised. Mass spectroscopy also demonstrates that this is not the case, and confirmed that the molecular weight of the compound to be at *m/z* = 213 and 211. The mass spectrum therefore indicates that the chlorine must have been retained, and the insolubility of the compound hints at a similar structure as before. The second possibility involves *ipso* attack of the imidoylketene and subsequent migration of the chlorine atom to the 3-position. From previous work (Chapter 2), imidoylketenes with *ortho*-chloro groups have been shown to attack at the site of the chlorine and for the chlorine to undergo a 1,5 sigmatropic shift to the 3-position. The third possibility involves attack at the other *ortho*- position, which could proceed via the following mechanism (Scheme **5.5**)



Scheme 5.5 Possible mechanism for attack of the imidoalkene

The main issue with the mechanism proposed in scheme **5.5** is that it involves a dipolar species with the positive charge on an atom adjacent to a carbonyl carbon atom, an electropositive centre. This structure is likely to be very high in energy and therefore unlikely to form.

The most likely structure for the product of the pyrolysis of **5.3** is the 3-chloropyrazinopyridinone **5.6** (Scheme **5.6**).

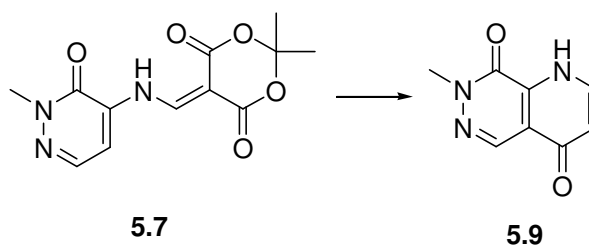


Scheme 5.6 Pyrolysis of compound **5.3**

Further evidence for this structure being the correct structure is shown in further work reported later on in this chapter.

5.2.2 Pyrolysis of Compounds **5.7** and **5.8**

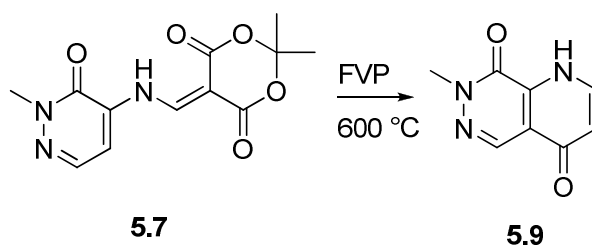
Pyrolysis of compound **5.7** would be expected to give the fused pyridine system **5.9** (Scheme **5.7**)



Scheme 5.7 Proposed pyrolysis of compound **5.7**

Upon pyrolysis of compound **5.7** two products could be observed forming in the trap, a white solid forming at the exit point of the furnace tube and a yellow solid forming at the U-tube bend. Distilling hot dichloromethane through the U-tube dissolved the yellow solid, leaving the white solid behind. The white solid was removed by suspension in acetone.

The white involatile solid was the expected product, the pyridone system **5.9**. This was found to adopt the keto tautomer by the coupling constants in the ^1H NMR spectrum (*ca* 7.5 Hz). This product was isolated in 19% yield (Scheme **5.8**).



Scheme 5.8 Pyrolysis of compound **5.7**

Concentration of the yellow solution gave a brown-yellow solid, isolated in 63% yield. The mass spectrum showed a mass of $m/z = 133$ for the molecular ion, 44 less than the other product. Losses of 44 Da in mass are generally attributed to loss of carbon dioxide. The ^1H NMR spectrum of the compound showed 4 protons in the aromatic region, along with the *N*-methyl group (Figure **5.5**).

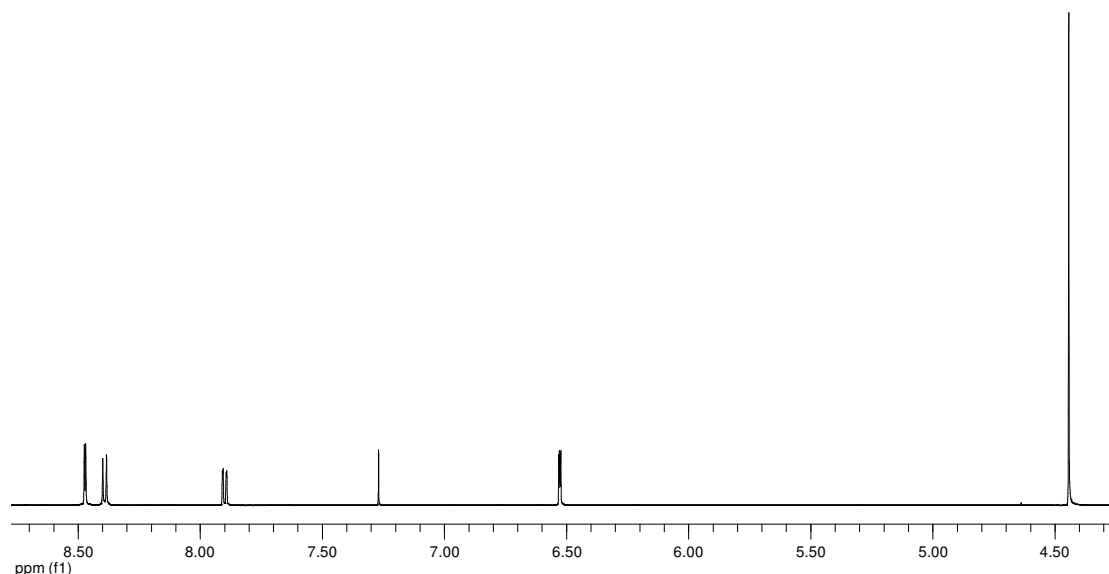


Figure 5.5 ^1H NMR spectrum of the unknown compound **5.11**

The protons at $\delta_H = 8.4$ and $\delta_H = 7.9$ ppm had coupling constants of *ca.* 5 Hz, typical of a pyridazine ring.¹²⁰ The coupling constants of the remaining two protons, at $\delta_H = 8.5$ and $\delta_H = 6.5$ ppm, were measured to be *ca.* 2.2 Hz. Small coupling constants of this magnitude in aromatic systems are typically associated with pyrrole type protons.⁹⁷ The ^{13}C NMR spectrum showed the presence of 7 carbon atoms: 4 CHs, 2 quaternary carbons and the *N*-methyl. No carbonyl signals were observed, with the highest quaternary carbon at $\delta_C = 148$ ppm. The proton/carbon connectivity was obtained from a HSQC experiment (Table **5.1**).

^{13}C signals	^1H signals
158.32	8.47
136.39	8.39
116.75	7.90
91.34	6.52
46.16	4.42
148.01	Quaternary
144.93	Quaternary

Table 5.1 HSQC Data of compound **5.11**

A NOESY experiment was performed and the spectrum is shown below (Figure **5.6**).

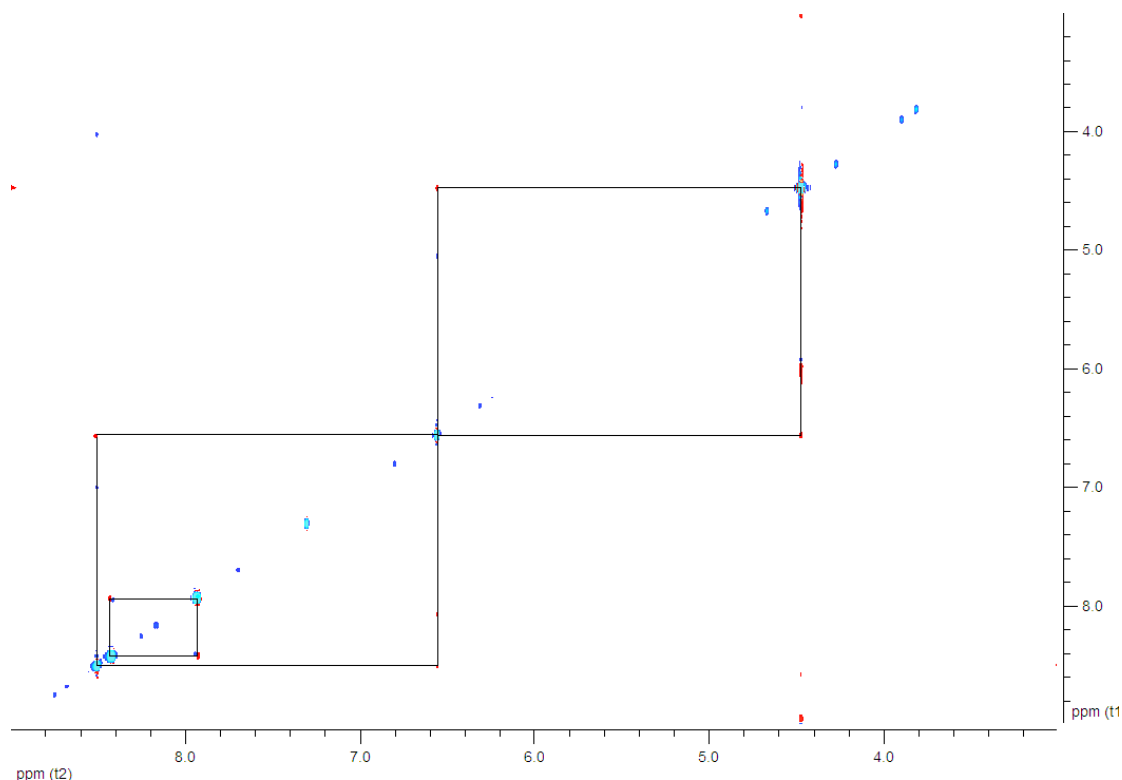


Figure 5.6 NOESY Spectrum of compound **5.11**

As can be seen from the NOESY spectrum in figure 5.6, the proton at $\delta_H = 6.5$ ppm shows an interaction with the methyl group at $\delta_H = 4.6$ ppm. A further NOE signal to the proton at $\delta_H = 8.5$ ppm identifies that it as being next to the doublet at $\delta_H = 6.5$ ppm. These data give us the structure shown in figure 5.7.

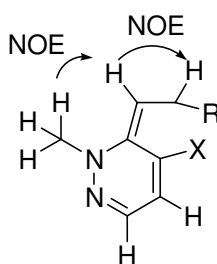


Figure 5.7 NOE Interactions in compound **5.11**

However X and R in figure 5.7 are unknown, but X is likely to be a nitrogen containing group derived from the amino group in the precursor. The ^{13}C spectrum shows only 7 resonances, with 2 quaternary carbons, 4 CH carbons and the methyl. Therefore to account for these data X and R in figure 5.7 must be the nitrogen atom from the amino group. This generates the pyrrolopyridazine **5.11** (figure 5.8).

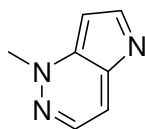
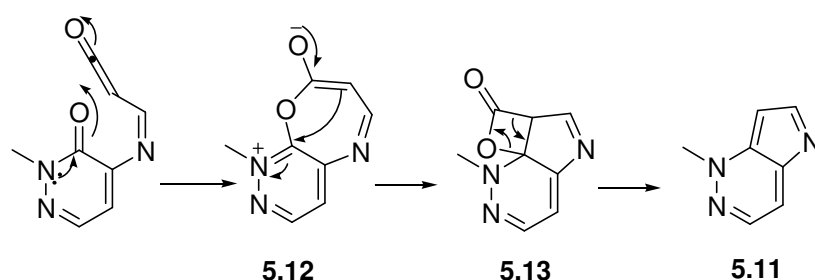


Figure 5.8 Structure of compound **5.11**

The pyrrolopyridazine ring system is a rare heterocyclic ring system, with only a few examples reported in the literature.¹²¹ These tend to *N*-unsubstituted, adopting the pyrrole *N*-H tautomer and feature further substitution in the ring skeleton. Examples of *N*-substituted pyrrolopyridazines are unknown in literature.

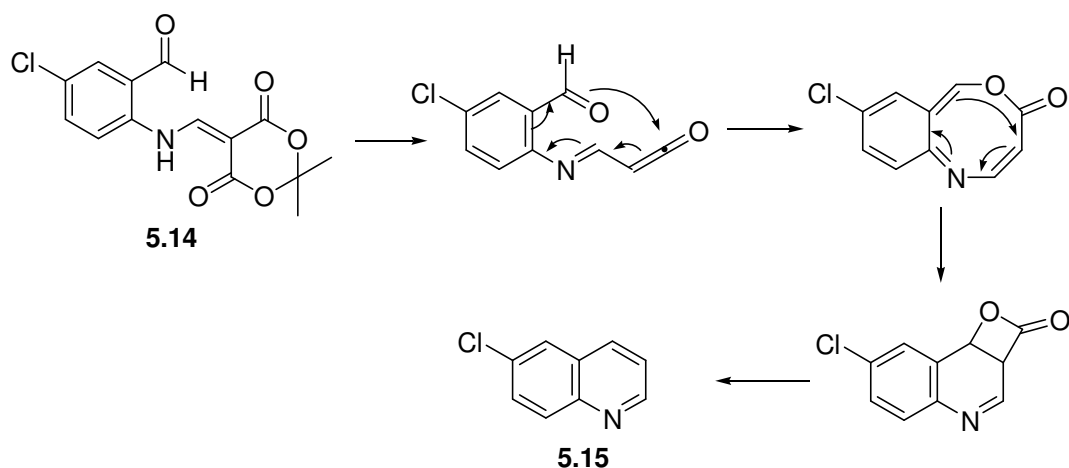
This hints at the ketene reacting at the pyridazinone carbonyl group and decarboxylating to give the pyrrole-type system. A plausible mechanism for its formation, is given in scheme **5.9** (below)



Scheme 5.9 Mechanism for the formation of compound **5.11**

Cyclisation of the carbonyl group into the ketene leads to the formation of the dipolar intermediate **5.12**. This can then undergo a second electrocyclicalization to give the β -lactone **5.13**, which can decarboxylate to give the pyrrolopyridazine **5.11** and carbon dioxide.

The type of electrocyclicalization-decarboxylation work has previously been observed,²⁴ with the pyrolysis of the methylene Meldrum's derivative of a 2-aminobenzaldehyde **5.14**. This led to the formation of 6-chloroquinoline **5.15** by a similar mechanism (Scheme **5.10**)



Scheme 5.10 Mechanism for the formation of 6-chloroquinoline **5.15**

In this example, the reaction forms an eight-membered ring intermediate rather than the dipolar seven-membered ring above, but the reaction mechanisms are similar. DFT calculations at B3LYP/6-31G** using Gaussian03⁸³ were employed in order to establish the energetics and feasibility of both mechanisms. The energy surface for the formation of 6-chloroquinoline from the aminobenzaldehyde precursor is shown in figure 5.9 (below).

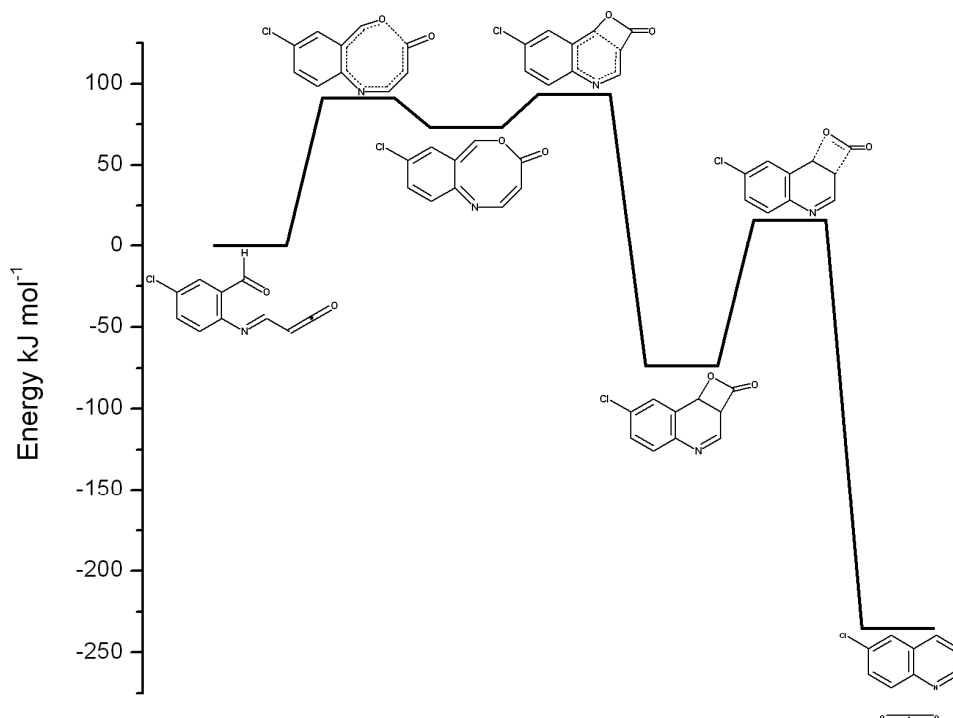


Figure 5.9 Energy surface for the formation of 6-chloroquinoline **5.15**

The initial electrocyclisation has an energy barrier of 91 kJ mol^{-1} , which leads to an

intermediate 73 kJ mol⁻¹ higher than the initial imidoylketene. However the second electrocyclisation proceeds *via* a much smaller energy barrier of 20 kJ mol⁻¹ to give the β -lactone, 74 kJ mol⁻¹ lower in energy than the imidoylketene. Decarboxylation preceeds *via* a 90 kJ mol⁻¹ barrier to give the two products, which have a combined energy that is 235 kJ mol⁻¹ lower than the initial ketene and providing a large thermodynamic driving force for the decarboxylation to occur.

DFT calculations were then applied to the electrocyclisation of compound **5.11** at B3LYP/6-31G** level and the energy surface obtained is shown below (Figure 5.10)

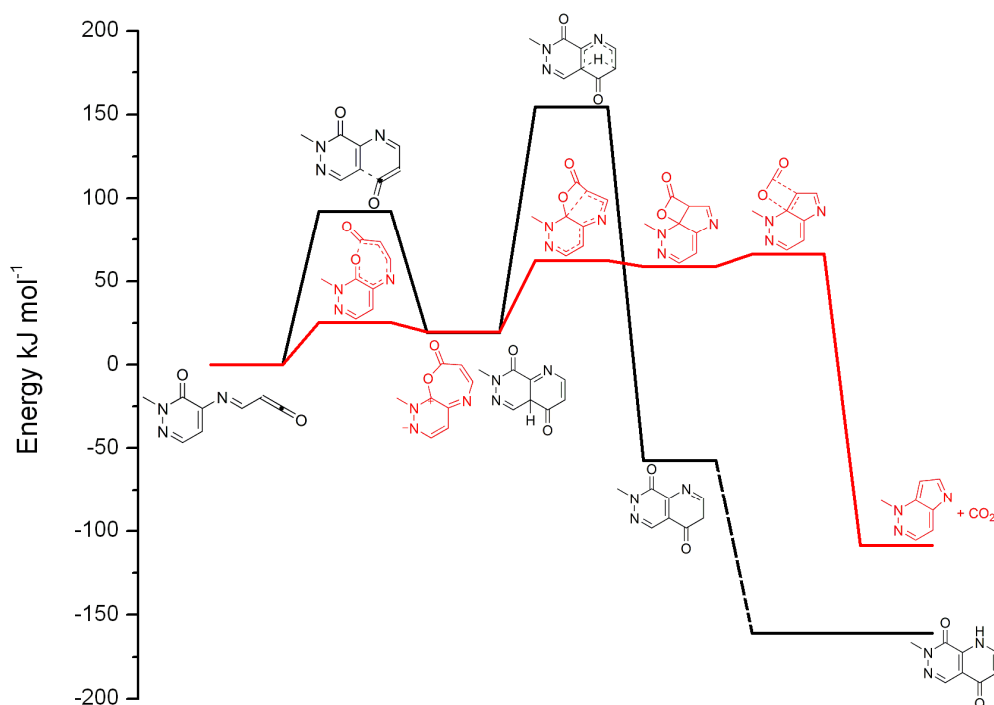


Figure 5.10 Energy surface for the formation of compounds **5.9** and **5.11**

The electrocyclisation mechanism (in black) follows a similar pattern to other examples of this reaction (see Chapter 2 and 3), with an initial barrier to the reaction (92.2 kJ mol⁻¹), followed by the rate determining 1,5 hydrogen shift with a larger energy barrier of 135.1 kJ mol⁻¹. As before the 1,3 hydrogen shift to the final product could not be modelled. The energy for the initial cyclisation is higher than those for the intial cyclisation in the quinolinone cyclisation (typically around 50 kJ mol⁻¹). The 1,5 hydrogen shift is of comparable energy, which typically around 120 kJ mol⁻¹

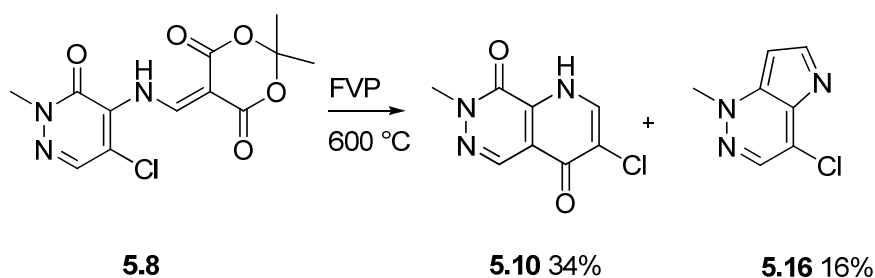
in the quinolinone energy surface.

The electrocyclisation-decarboxylation mechanism (in red) has a small barrier to form the 7,6 ring intermediate **5.12** of 25.3 kJ mol⁻¹. Formation of the 6,5,4 tricyclic intermediate **5.13** has a barrier of 110.5 kJ mol⁻¹, and decarboxylation has a barrier of 7.7 kJ mol⁻¹ to give the product **5.11** and carbon dioxide.

From figure 5.10, we can see that the energy for the electrocyclisation-decarboxylation mechanism (in red in Figure **5.10**) is lower for than the standard electrocyclisation mechanism (in black in Figure **5.10**). This is reflected in the yields of the two products obtained.

In comparison to the formation of 6-chloroquinolinone, the energies for the transition states are lower, but this may be a consequence of the difference in ring size formed (7 vs. 8). Also the energy of the β -lactone intermediate is higher in energy for the 7-membered ring system than for the 8-membered ring system, presumably due to the steric hinderance involved.

Pyrolysis of the chloro compound **5.8** lead again to the formation two products, with similar solubilities to the previous two products, in a 38:62 ratio of **5.16** to **5.10** (Scheme **5.11**).



Scheme 5.11 Pyrolysis of compound **5.8**

The pyrrolopyridazine **5.16** was obtained in 16% yield and required purification by column chromatography to separate it from other soluble impurities. The expected fused pyridinone **5.10** was obtained in 34% yield, and required no further purification. Of interest is the location of the chlorine atom in the molecule. As with the pyrolysis

of the *o*-chloroaniline methylene Meldrum's derivative in chapter 4, the chlorine atom migrates to the 3 position of the molecule by a 1,5 sigmatropic shift and is a further example of this type of shift. This also provides further evidence for the structure of compound **5.6**, which proved insoluble, and that the chlorine sigmatropic most likely occurred in that example as well.

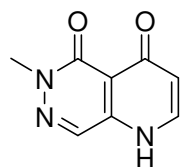
Conclusion

Pyrolysis of compounds **5.1** – **5.3** showed standard reactivity with the formation of pyrido[2,3-*d*]pyridazine-4,5-diones **5.4** – **5.6** in good yields. With a chloro substituent in the *ortho* position, the chlorine undergoes a 1,5 sigmatropic shift to the 3-chloro substituted product. These products are novel, with no examples of pyridazinopyridine-diones reported in the literature.

Pyrolysis of compounds **5.7** and **5.8** showed two different reactions to give two different products. The standard electrocyclisation mechanism was observed to give pyrido[2,3-*d*]pyridazine-4,8-diones **5.9** and **5.10**, again with an *ortho* chlorine substituent, migration of the chlorine atom was observed to give the 3-chloro product. A second mechanism, which involves the formation and contraction of a 7-membered ring intermediate and subsequent decarboxylation was found to give pyrrolo[3,2-*c*]pyridazines **5.11** and **5.16**. DFT calculations at B3LYP/6-31G** level show that both mechanisms are energetically feasible. This ring system is rare in the literature, with no *N*-substituted examples, and are often heavily substituted.

Experimental

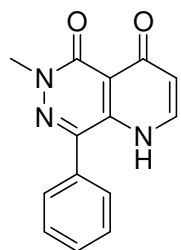
Pyrolysis of 2,2-Dimethyl-5-[(1-methyl-6-oxo-1,6-dihydro-pyridazin-4-ylamino)-methylene]-[1,3]dioxane-4,6-dione **5.1**



Pyrolysis of compound **5.1** (w 0.1035 g, T_f 600 °C, T_i 210 °C, P $2.5 - 2.7 \times 10^{-2}$ Torr, t 0.5 h) gave 6-Methyl-1*H*,6*H*-pyrido[2,3-*d*]pyridazine-4,5-dione **5.4** as a pale yellow solid (0.0459 g, 70%); mp 244 – 246 °C; (Found M^+ 177.05350, $C_8H_7N_3O_2$ requires 177.05328); δ_H (360 MHz, d_6 -DMSO, 80 °C) 8.42 (1H, s, br), 8.23 (1H, s, br), 7.09 (1H, s, br) and 3.77 (3H, s); Not soluble enough in d_6 -DMSO to acquire ^{13}C NMR data; m/z 177 (M^+ , 100%), 149 (37), 121 (11) and 106 (13).

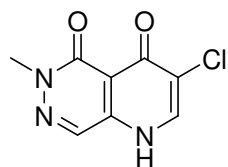
Addition of TFA to the DMSO sample sharpened the signals to give the following spectrum: δ_H (d_6 -DMSO + TFA) 8.77 (1H, d, 3J 6.0), 8.49 (1H, s), 7.15 (1H, d, 3J 5.9) and 3.74 (3H, s)

Pyrolysis of 2,2-Dimethyl-5-[(1-methyl-6-oxo-3-phenyl-1,6-dihydro-pyridazin-4-ylamino)-methylene]-[1,3]dioxane-4,6-dione **5.2**



Pyrolysis of compound **5.2** (w 0.250 g, T_f 600 °C, T_i 200 °C, P 2.3×10^{-2} Torr, t 35 min.) gave 6-Methyl-8-phenyl-1*H*,6*H*-pyrido[2,3-*d*]pyridazine-4,5-dione **5.5** as an off white solid (0.141 g, 96%); mp 163 – 165 °C; (Found M^+ 253.08459; $C_{14}H_{11}N_3O_2$ requires 253.08458); δ_H (d_6 -DMSO) 8.87 (1H, d, 3J 5.3), 8.01 – 7.92 (2H, m), 7.55 – 7.51 (3H, m), 7.26 (1H, d, 3J 5.3) and 3.87 (3H, s); δ_C (d_6 -DMSO) 166.24 (quat), 162.50 (quat), 156.86, 147.57 (quat), 146.29 (quat), 133.95 (quat), 130.06 (2CH), 129.21, 127.84 (2CH), 112.12, 111.60 (quat) and 38.71 (CH_3); m/z 253 (M^+ , 100%), 252 (62).

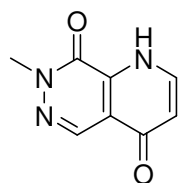
Pyrolysis of 2,2-Dimethyl-5-[(1-methyl-6-oxo-5-chloro-1,6-dihydro-pyridazin-4-ylamino)-methylene]-[1,3]dioxane-4,6-dione **5.3**



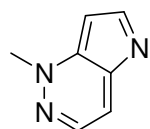
Pyrolysis of compound **5.3** (w 0.116 g, T_f 600 °C, T_i 210 °C, P 2.3 – 2.6×10^{-2} Torr, t 0.75 h) gave 3-Chloro-6-methyl-1*H*,6*H*-pyrido[2,3-*d*]pyridazine-4,5-dione **5.6** as a yellow-white solid (0.0640 g, 85%); mp 302 – 304 °C (decomp.); (Found M^+ 211.01445, $C_8H_6N_3O_2Cl$ requires 211.01431); Compound proved insoluble in DMSO and NMR data not acquired.; m/z 213 (M^+ , 34%), 211 (M^+ , 100), 177 (83), 159 (70), 136 (57) and 105 (49)

Pyrolysis of 2,2-Dimethyl-5-[(2-methyl-3-oxo-2,3-dihydro-pyridazin-4-ylamino)-methylene]-[1,3]dioxane-4,6-dione **5.7**

Pyrolysis of compound **5.7** (w 0.1033 g, T_f 600 °C, T_i 190 °C, P $2.2 - 2.3 \times 10^{-2}$ Torr, t 0.75 h) gave two products, a white solid formed at the quickfit joint and a yellow solid formed at the u-tube bend. The yellow solid was dissolved in DCM and the solution removed from the u-tube. The white solid was suspended in acetone, and removed from the u-tube. Removal of the solvents gave a white solid, 7-Methyl-1,7-dihydro-pyrido[2,3-*d*]pyridazine-4,8-dione **5.9** (0.0127 g, 19%), and a brown-yellow solid, 1-Methyl-1*H*-pyrrolo[3,2-*c*]pyridazine **5.11** (0.0308 g, 63%).



7-Methyl-1,7-dihydro-pyrido[2,3-*d*]pyridazine-4,8-dione **5.9** mp >310 °C; (Found M^+ 177.05318; $C_8H_7N_3O_2$ requires 177.05328); δ_H (360 MHz, d_6 -DMSO) 8.32 (1H, s), 7.90 (1H, d, 3J 7.5), 6.44 (1H, d, 3J 7.5) and 3.79 (3H, s); δ_C (90 MHz, d_6 -DMSO) 175.25 (quat), 155.16 (quat), 140.18, 136.27 (quat), 133.47, 119.80, 117.60 (quat) and 39.39 (CH_3); m/z 177 (M^+ , 13%), 159 (27), 136 (100), 120 (12), 105 (91) and 91 (45)

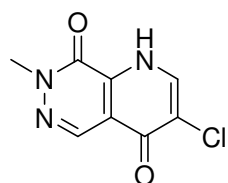


1-Methyl-1*H*-pyrrolo[3,2-*c*]pyridazine **5.11** mp 64 - 66 °C; (Found M^+ 133.06353, $C_7H_7N_3$ requires 133.06345); δ_H (360 MHz) 8.47 (1H, d, 3J 2.2), 8.39 (1H, d, 3J 5.4), 7.90 (1H, dd, 3J 5.4, 4J 0.7), 6.52 (1H, dd, 3J 2.2, 4J 1.1) and 4.42 (3H, s); δ_C (90 MHz) 158.32, 148.01 (quat), 144.93 (quat),

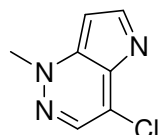
136.39, 116.75, 91.34 and 46.16 (CH₃); *m/z* 133 (M⁺, 6%), 91 (6), 75 (6), 66 (26), 52 (44), 28 (100).

Pyrolysis of 2,2-Dimethyl-5-[(2-methyl-3-oxo-2,3-dihydro-pyridazin-4-ylamino)-methylene]-[1,3]dioxane-4,6-dione **5.8**

Pyrolysis of compound **5.8** (w 0.252 g, *T_f* 600 °C, *T_i* 200 °C, *P* 2.8 – 3.0 × 10⁻² Torr, *t* 11 min) gave two solids, one white forming at the quickfit joint and one yellow solid forming just after it. The whole pyrostate was washed out with methanol, and the insoluble white solid filtered off to give 3-Chloro-7-methyl-1,7-dihydro-pyrido[2,3-*d*]pyridazine-4,8-dione **5.10** (0.0573 g, 34%). The solution was absorbed onto alumina column chromatography (alumina, ethyl acetate) and gave 4-Chloro-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridazine **5.16** as an orange solid (0.0214 g, 16%)



3-Chloro-7-methyl-1,7-dihydro-pyrido[2,3-*d*]pyridazine-4,8-dione **5.10**; mp >310 °C; (Found M⁺ 211.01416, C₈H₆N₃O₂Cl requires 211.01431) δ_H (360 MHz, *d*₆-DMSO) 13.01 (1H, br, s), 8.37 (1H, s), 8.31 (1H, s) and 3.79 (3H, s); δ_C (90 MHz, *d*₆-DMSO) 169.71 (quat), 154.96 (quat), 138.56, 135.43 (quat), 133.78, 123.59 (quat) and 39.52 (CH₃); *m/z* 213 (M⁺, 33%), 211 (M⁺, 100), 183 (53), 159 (66) and 135 (72)



4-Chloro-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridazine **5.16**; mp 55 – 57 °C; (Found M⁺ 167.02473; C₇H₆N₃Cl requires 167.02448); δ_H 8.43 (1H, d, ³*J* 2.0), 8.35 (1H, s), 6.53 (1H, d, ³*J* 2.0) and 4.51 (3H, s); δ_C 158.07, 144.84 (quat), 136.05, 126.23 (quat), 105.43 (quat), 98.90 and 45.99 (CH₃); *m/z* 169 (M⁺, 30%), 167 (M⁺, 100) and 104 (13).

Chapter 6

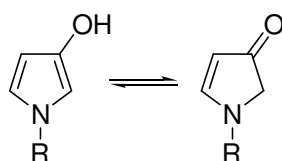
Synthesis of

***N*-Unsubstituted 3-Hydroxypyrroles**

and 1*H*-Pyrrol-3(2*H*)-ones by FVP

6.1 Introduction

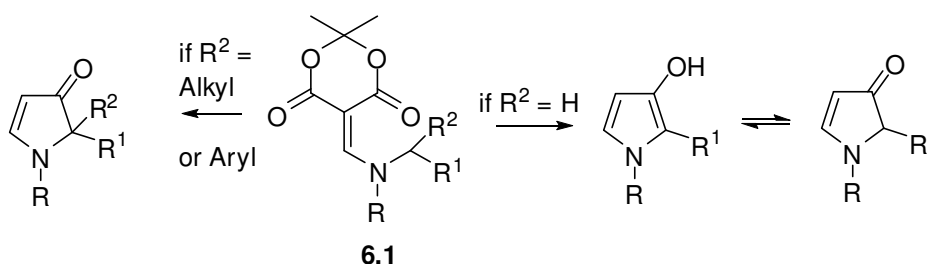
3-Hydroxypyrroles are difficult to synthesise and handle, mainly due to their sensitivity towards air oxidation. These compounds are highly electron-rich and can exist in two distinct tautomers:¹²² the 3-hydroxypyrrole and 1*H*-pyrrol-3(2*H*)-one tautomers (Scheme 6.1). ‘Pyrrolone’ and ‘Hydroxypyrrole’ in this chapter refer exclusively to the 3-isomers.



Scheme 6.1 3-Hydroxypyrrole and 1*H*-pyrrol-3(2*H*)-one tautomers

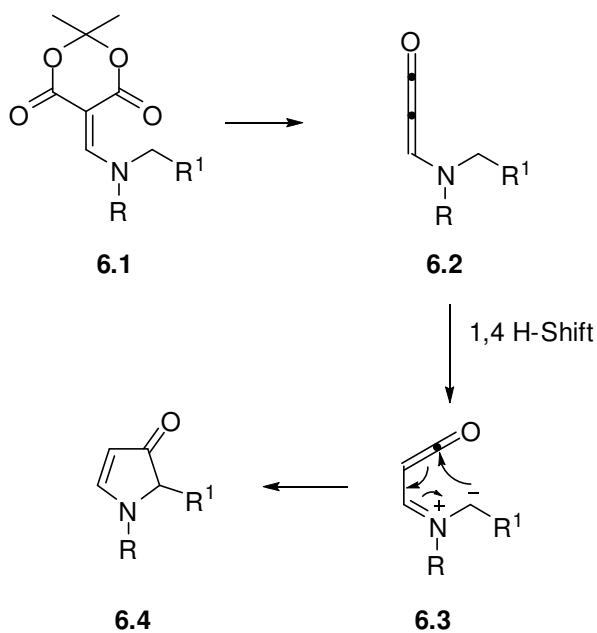
Previously they have been synthesised by a variety of methods, such as Dieckmann condensation reactions.¹²³ A review of pyrrolones has been published, encompassing both the synthesis of and properties of pyrrolones.¹²⁴ This review aims to focus on the synthesis of 3-hydroxypyrroles from the pyrolysis of Meldrum's acid derived precursors.

The precursors are based on structure 6.1, where R and R¹ can be alkyl or aryl groups, pyrolysis of such compounds under FVP conditions gives *N*-substituted hydroxypyrroles or pyrrolones (Scheme 6.2)



Scheme 6.2 Pyrolysis of compound 6.1

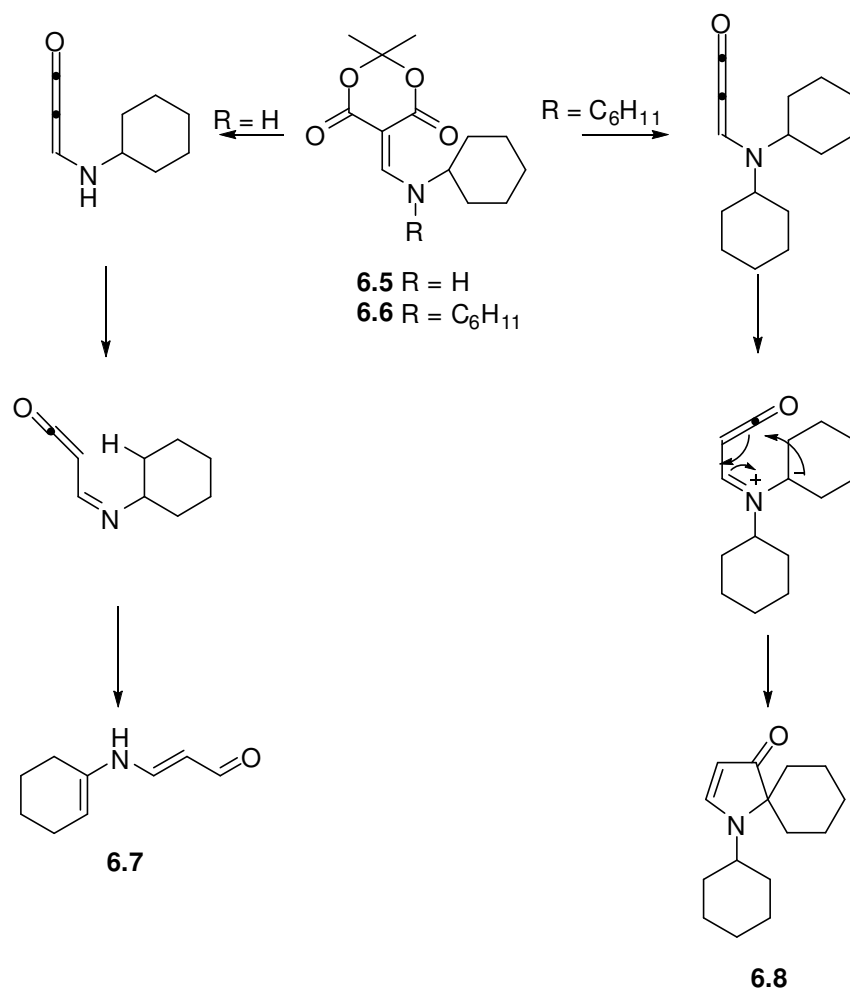
The mechanism for the formation of the hydroxypyrroles is shown in scheme 6.3 (below)



Scheme 6.3 Mechanism for the pyrolysis of compound **6.1**

Loss of acetone and carbon dioxide generate the methyleneketene **6.2**, which undergoes a 1,4 hydrogen shift to give the azomethine ylide **6.3**. Cyclisation of this intermediate yields the product as the pyrrolone tautomer **6.4**.

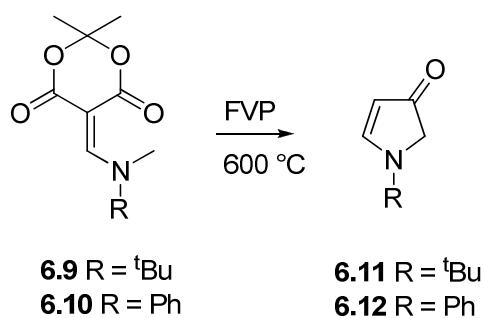
All of the examples shown here follow this basic mechanism to give 3-hydroxypyroles and, to date, have only been shown to give *N*-substituted 3-hydroxypyroles. When R is a hydrogen atom, a competitive 1,3 hydrogen shift can occur to give an imidoalkene.¹²⁵ This is demonstrated in the pyrolysis of the cyclohexyl derivatives **6.5** and **6.6** (Scheme 6.4).



Scheme 6.4 Pyrolysis of cyclohexyl derivatives **6.5** and **6.6**

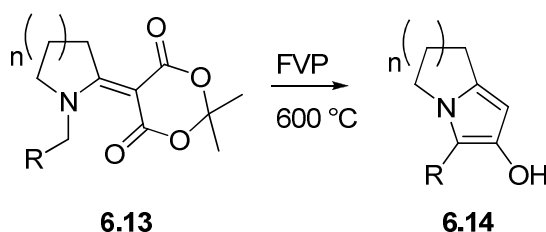
With R is a hydrogen atom, the isolated product was 3-(cyclohex-1-enylamino)-propenal **6.7**, whereas when R was cyclohexyl, the pyrrolone **6.8** was obtained. Deuteriation experiments of the dicyclohexyl precursor proved that the 1,4 hydrogen shift occurs.

The scope of the reaction was also explored, varying the groups on the amine.¹²⁶ A wide range of alkyl chains, both linear and branched were tolerated, as were rings (cyclohexyl or cycloheptyl). The pyrolysis of *N*-methyl-*N*-tert-butylamine or *N*-methyl-*N*-phenylamine derived compounds **6.9** and **6.10** gave 1-substituted pyrrolones **6.11** and **6.12** (Scheme 6.5).



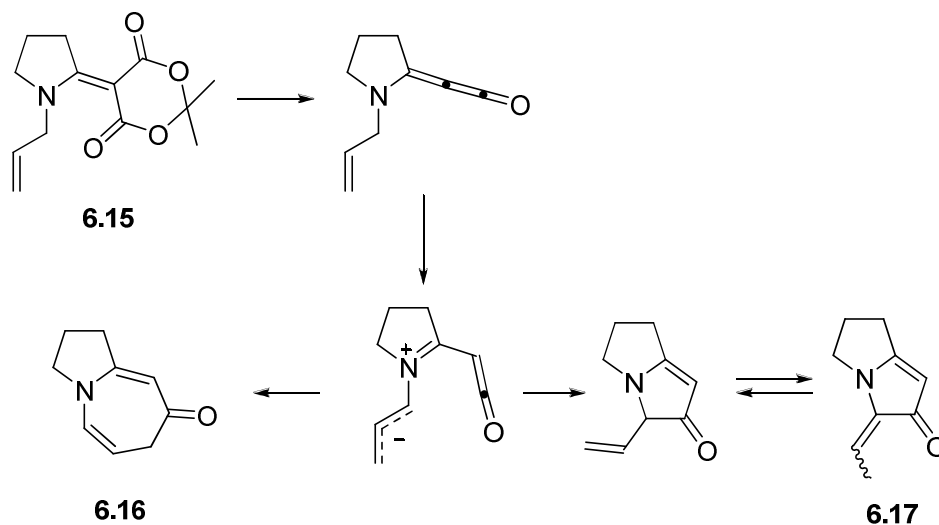
Scheme 6.5 Pyrolysis of compounds **6.9** and **6.10**

This methodology was also extended to the synthesis of bicyclic [*n*.3.0] hydroxypyrroles **6.14**, derived from the pyrolysis of cyclic precursors such as **6.13** (Scheme 6.6).¹²⁷



Scheme 6.6 Pyrolysis of compound **6.13**

The first report focussed on the R group being an allyl (compound **6.15**), the pyrolysis of which gave a by-product, the azepinone **6.16**, as well as the hydroxypyrrole **6.17**. The azepinone **6.16** is formed from an electrocyclicisation of the terminal end of the allyl group (scheme 6.7)



Scheme 6.7 Pyrolysis of compound **6.15**

This work was then expanded to explore the scope of the reaction.¹²⁸ The ring size, *n*, was variable from 1 to 3 giving (5,5), (5,6) and (5,7) ring systems isolated in good yields (~70 – 80% after purification). Variations on the R group were also tolerated with hydrogen, methyl, phenyl and esters all giving the cyclised products in similar yields.

The most important 3-oxygenated pyrroles are the prodigiosins, a range of natural products, which have immunosuppressive activity at low dosage.¹²⁹ The structure of prodigiosin possesses an alkoxyppyrole core and one example has the structure shown in figure 6.1.

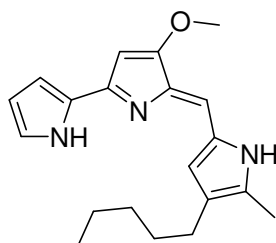
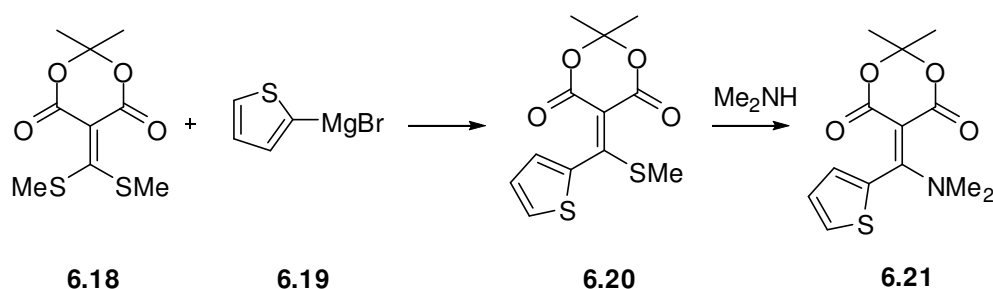


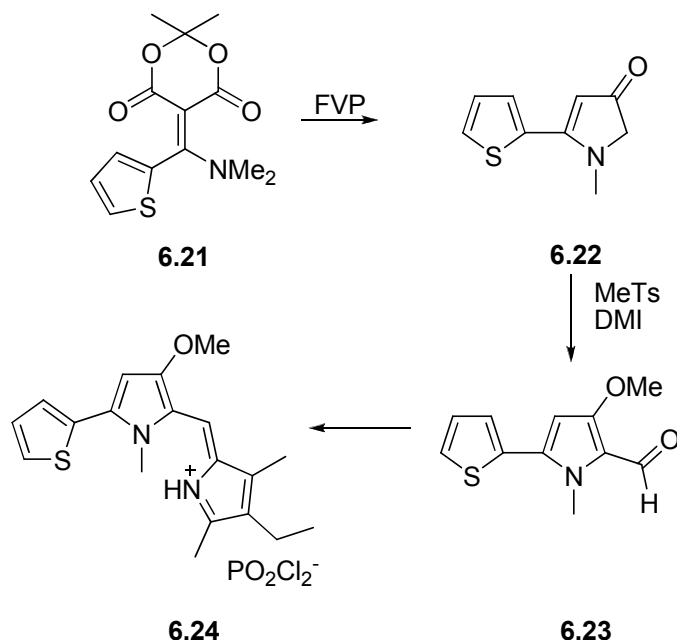
Figure 6.1 Structure of Prodigiosin

It can be envisaged that the cyclisation of Meldrum's acid precursors to give 3-hydroxypyrroles could be applied to a total synthesis of prodigiosin. Analogues of prodigiosin have been synthesised by this methodology.¹³⁰ The cyclisation precursor **6.21** can be synthesised by addition of dimethylamine to compound **6.20**, which can be synthesised from Grignard addition of thiophene-2-magnesium bromide **6.19** to compound **6.18** (Scheme 6.8).



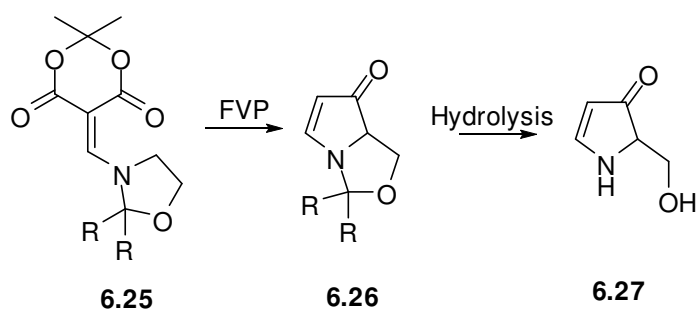
Scheme 6.8 Synthesis of compound **6.21**

Pyrolysis of compound **6.21** gives the 5-thienylpyrrolone **6.22** in 70% yield. Alkylation and Vilsmeier formation gives the 2-formylpyrrole **6.23**, which can be coupled with kryptopyrrole to give the prodigiosin analogue **6.24** (Scheme 6.9)



Scheme 6.9 Synthesis of compound **6.24**

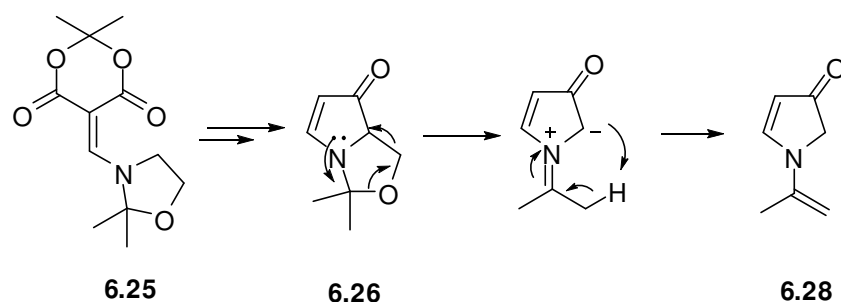
In a further attempt to synthesise the alkoxy core of prodigiosin using this methodology,¹³¹ it was anticipated that pyrolysis of oxazolidine-derived compound **6.25** would give the bicyclic pyrrolone **6.26**, which could be easily hydrolysed to give the *N*-unsubstituted pyrrolone **6.27** (Scheme 6.10)



Scheme 6.10 Proposed synthesis of compound **6.27**

However upon pyrolysis, none of compound **6.27** was observed and only *N*-alkenylpyrrolone **6.28** was observed. The mechanism for its formation involves the formation of the bicyclic product **6.26**, which then opens by loss of formaldehyde

give the observed product, and the mechanism was supported by deuteration of the oxazolidine ring (Scheme 6.11)



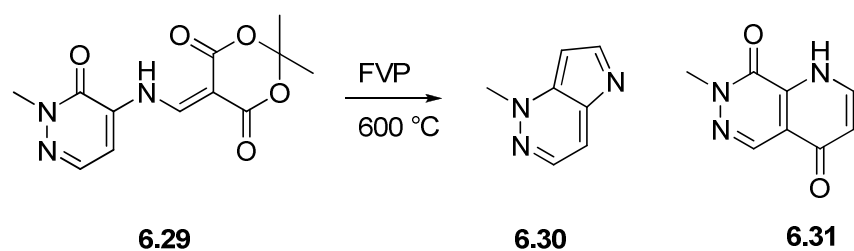
Scheme 6.11 Mechanism of the formation of compound **6.28**

Overall the ‘Meldrum’s acid’ route to pyrrolones has been versatile and one of the simplest routes to these hard-to-obtain compounds. However no examples of *N*-unsubstituted hydroxypyrroles or pyrrolones have been published by this method, since the pyrolysis of the precursors proceeds via a 1,3 hydrogen shift to give imidoalkenes.

6.2 Discussion

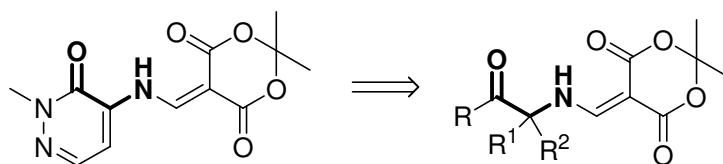
6.2.1 Introduction

In the previous chapter, the pyrolysis of compound **6.29** lead to the formation of compound **6.30** by an electrocyclisation-decarboxylation mechanism, as well as the expected product **6.31** (Scheme 6.12).



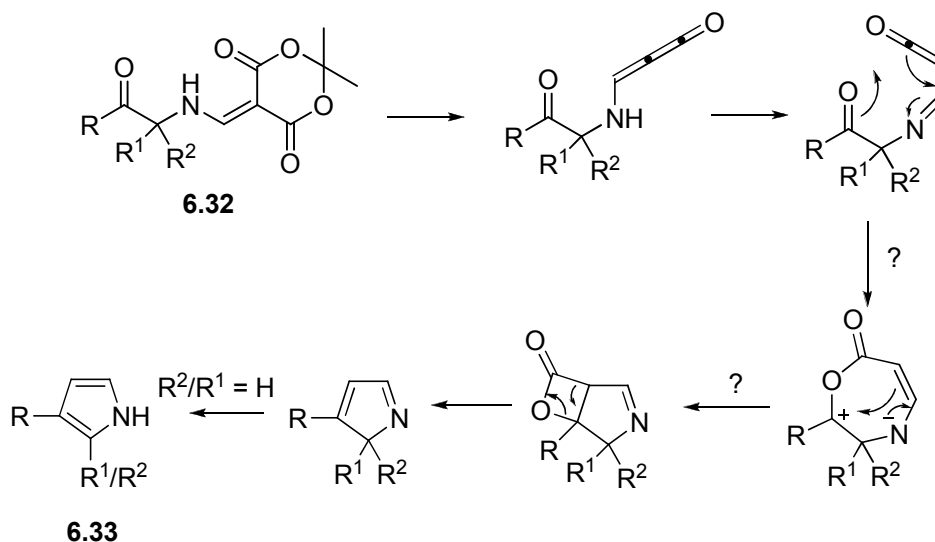
Scheme 6.12 Pyrolysis of compound **6.29**

In order to discover other reactions that proceed *via* a similar mechanism, a model reaction was needed. If the features of compound **6.29** are examined in detail, then the only required feature is apparently separation of the amine and the carbonyl by a one carbon unit (Scheme 6.13)



Scheme 6.13

Pyrolysis of this precursor **6.32** might therefore proceed *via* the mechanism shown in scheme **6.14**, giving the pyrrole product **6.33**.

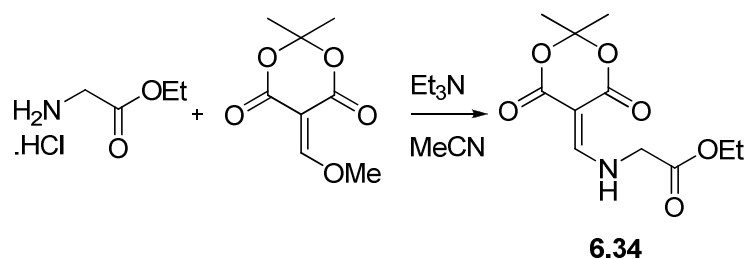


Scheme 6.14 Potential mechanism for the formation of pyrrole **6.33**

Upon pyrolysis, formation of an methyleneketene followed by a 1,3 hydrogen shift should give an imidoylketene. Cyclisation of the imidoylketene might occur to give a 7-membered ring, which might undergo a ring contraction to give a bicyclic system. This can decarboxylate to give the *2H*-pyrrole, which tautomerises to give the pyrrole.

For the model reaction, in order to synthesise the precursor **6.32**, the appropriate amine or its salt must be readily available. Aminoacetone is not commercially available and aminoacetaldehyde is only commercially available as its dimethylacetal. Glycine and its amide and esters are commercially available, either as their hydrochloride salts or free bases. The ester was chosen as the model system since amides and acids tend to be less volatile.

The starting material **6.34** was synthesised using a known route for preparing Meldrum's acid derivatives from amine salts.¹³² The precursor **6.34** was isolated in 77% yield from glycine ethyl ester as a yellow solid (Scheme **6.15**)



Scheme 6.15 Synthesis of compound **6.34**

Pyrolysis of compound **6.34**, if the mechanism proposed in scheme **6.14** is correct, should give 3-ethoxypyrrole as the product. Upon pyrolysis of the compound, at 600 °C, a brown oil was obtained. Distillation of the brown oil gave a yellow oil, which solidified over time. However from its ^1H NMR spectrum, the expected 3-ethoxypyrrole was not observed. Although the presence of an ethyl group was seen in the ^1H NMR spectrum, there was 1 less pyrrole-type peak than required and the mass spectrum of the compound showed a molecular ion at $m/z = 155$. The structure of the compound was confirmed by comparison with a published spectra of a known compound,¹ ethyl 3-hydroxypyrrole-2-carboxylate **6.35**, which was isolated in 85% yield from the pyrolysis (Figure **6.2**).

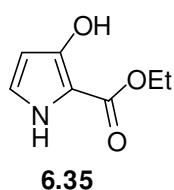
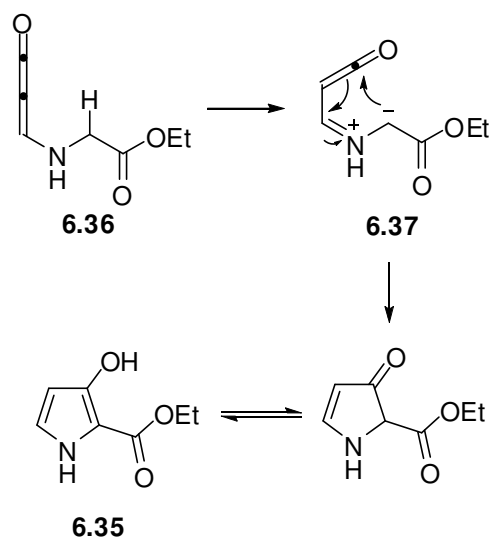


Figure 6.2 Structure of compound **6.35**

The mechanism for the formation of compound **6.35** is from the methyleneketene **6.36**, which can undergo a 1,4 hydrogen transfer to give the azomethine ylide **6.37**. Intermediate **6.37** can then undergo an electrocyclicalisation to give the pyrrolone product, a tautomer of the observed product **6.35** (Scheme **6.16**)



Scheme 6.16 Mechanism for the formation of compound **6.35**

As described above, this type of cyclisation has only been observed for *N,N*-

disubstituted methylene Meldrum's acid precursors. This is the first example of this type of pyrolysis giving an *N*-unsubstituted hydroxypyrrole from a Meldrum's acid precursor. The typical reaction of methyleneketenes such as **6.36** is to undergo a 1,3 hydrogen shift to give the imidoalkene. This mechanism is further demonstrated by deuteration experiments. Pyrolysis of the *N*-deuterated analogue of compound **6.34** shows no incorporation of deuterium in the product after work-up. Should the standard 1,3 hydrogen shift occur, to give the imidoalkene, then incorporation of deuterium into the 4-position of compound **6.35** would be expected.

In order to demonstrate the feasibility of this mechanism, DFT calculations were employed. Using Gaussian03,⁸³ the intermediates, transition states and products were all calculated to B3LYP/6-31G** level, with transition states calculated to first order (one imaginary frequency). These calculations will also include the typical reaction mode of methyleneketenes, to undergo 1,3 hydrogen shifts to generate imidoalkenes. The energy surface for the two mechanisms is shown below (Figure 6.3)

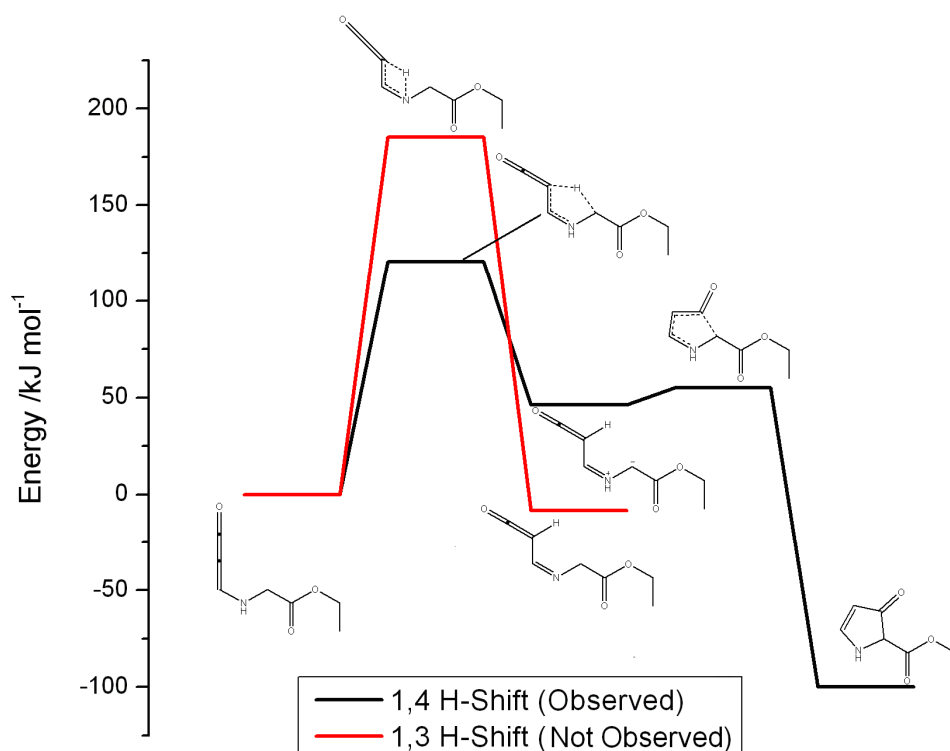
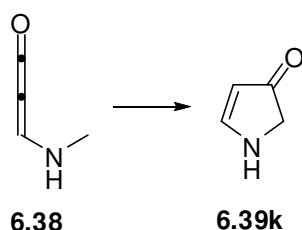


Figure 6.3 Energy surface of the mechanism for the formation of compound **6.35**

From figure 6.3, the reason why the methyleneketene **6.36** undergoes the 1,4

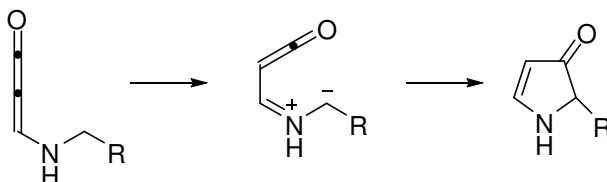
hydrogen shift over the 1,3 hydrogen shift becomes apparent. The barrier to the 1,4 hydrogen shift is approximately 50 kJ mol^{-1} lower in energy than the corresponding 1,3 shift, even though the 1,3 shift leads to the lower energy intermediate. The barrier to the electrocyclisation is small, approximately 10 kJ mol^{-1} and leads to the product, which in its pyrrolone form, is 100 kJ mol^{-1} lower in energy than the initial ketene.

Calculations by Wentrup¹³³ on the formation of pyrrolones have focussed on the cyclisation to 1*H*-pyrrol-2(3*H*)-one **6.39k** from methyleneketene **6.38** (Scheme **6.17**)



Scheme 6.17

The energies obtained by Wentrup are shown in table **6.1**, with the results obtained for the corresponding ester example included for comparison.



Scheme 6.18

Species	R = H	R = COOEt
Methyleneketene	0	0
1,4 H-Shift TS	163.5	120.5
Azomethine Ylide	102.9	46.2
Cyclisation TS	106.7	55.2
Pyrrolone	-110.9	-100

Table 6.1 Energies for the formation of pyrrolones (Energies are in kJ mol^{-1} , relative to the initial methyleneketene)

The two energy surfaces are shown on figure 6.4 (below)

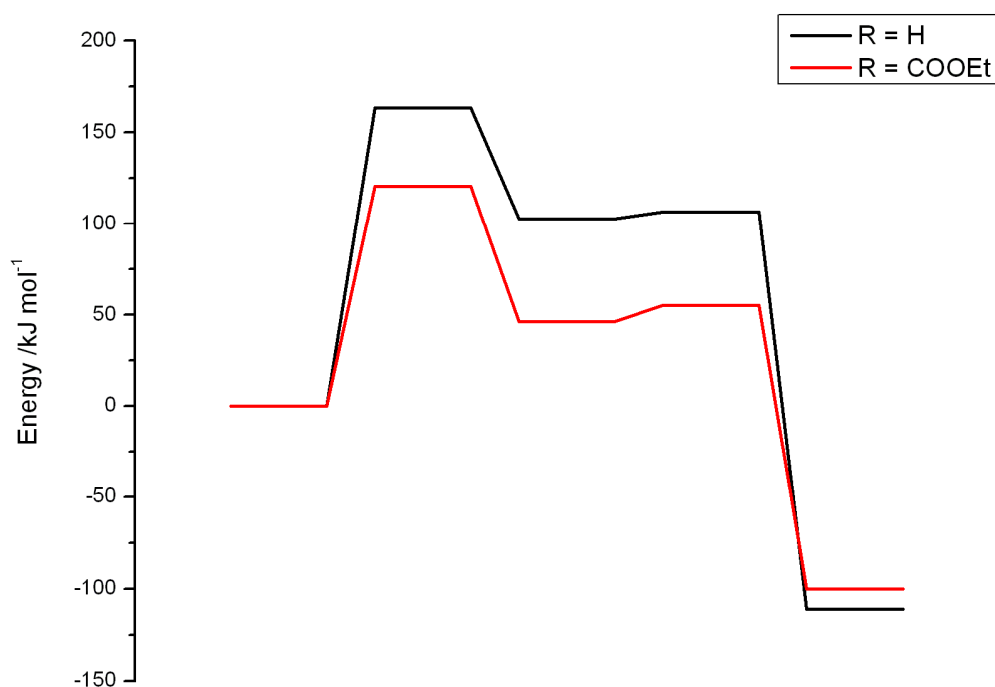
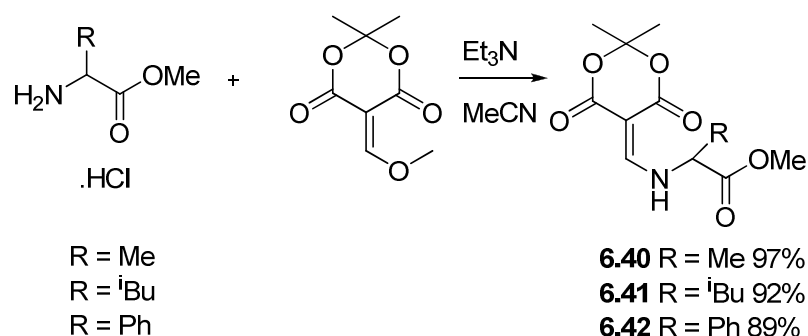


Figure 6.4 Energy surface of the mechanism for the formation of pyrrolones **6.35** and **6.39k**

From figure 6.4, the effect of the ester group on the energies of the intermediates and transition states is apparent. The energies are lowered by a significant amount favouring the formation of the azomethine ylide **6.37**, and the observed products.

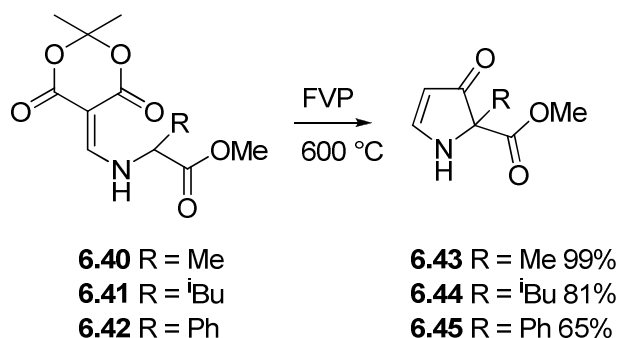
6.2.2 Further Examples

Since the starting material was an ester of the amino acid, glycine, then more examples of this type of cyclisation can be obtained by simply employing other amino acids. Precursors derived from alanine (**6.40**, R = Me), leucine (**6.41**, R = ⁱBu) and phenylglycine (**6.42**, R = Ph) and methoxymethylene Meldrum's acid were synthesised in good yields (Scheme 6.19).



Scheme 6.19 Synthesis of compounds **6.40** – **6.42**

Pyrolysis of compounds **6.40** – **6.42** at 600 °C gave the 2,2-disubstituted pyrrolones **6.43** – **6.45** in good to excellent yields, without the need for further purification (Scheme 6.20)



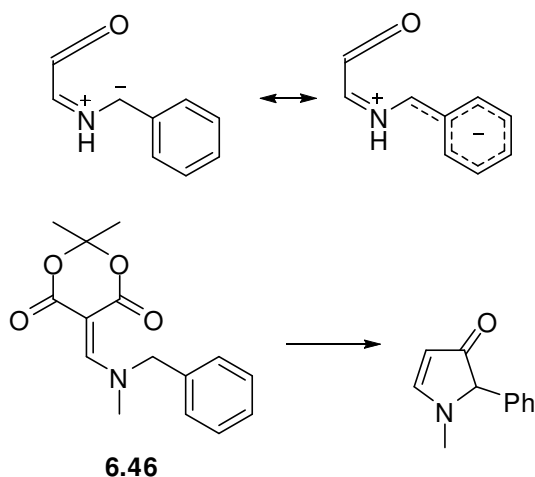
Scheme 6.20 Pyrolysis of compounds **6.40** – **6.42**

Although the chirality of the final pyrrolone was not tested for the presence of an excess of one of the two possible enantiomers, previous work has shown that chiral centre partially racemises during the pyrolysis.¹³⁴ Using amino acid based precursors, *N*-unsubstituted 3-hydroxypyrroles and pyrrolones have been synthesised in good yields under FVP conditions for the first time.

6.2.3 Non Ester-Based Cyclisations

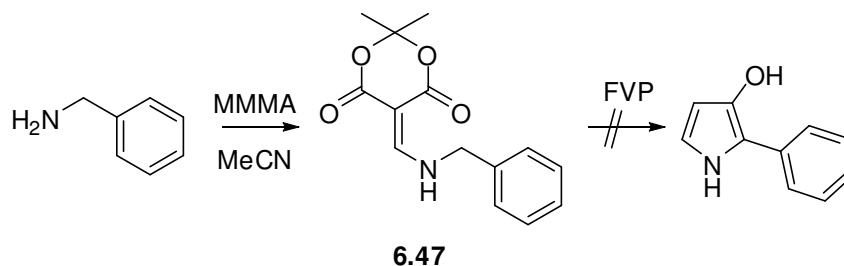
The work so far has used an ester as the group to stabilise the azomethine ylide intermediate formed. It can therefore be envisaged that other groups could potentially stabilise the intermediates and transition states formed, diverting the reaction from the 1,3 hydrogen shift to the 1,4 hydrogen shift, giving the 3-hydroxypyrrole products.

Phenyl groups could potentially stabilise the ketene by delocalisation of the charge into the aromatic ring (Scheme 6.21), and indeed it is found that *N*-alkyl-*N*-benzyl derivative **6.46** preferentially cyclises onto the CH₂ of the benzyl group.



Scheme 6.21

The starting material **6.47** was synthesised using benzylamine and methoxymethylene Meldrum's acid. The pyrolysis of compound **6.47**, however, gave a complex mixture of products with no identifiable pyrrole-like products (Scheme 6.22).

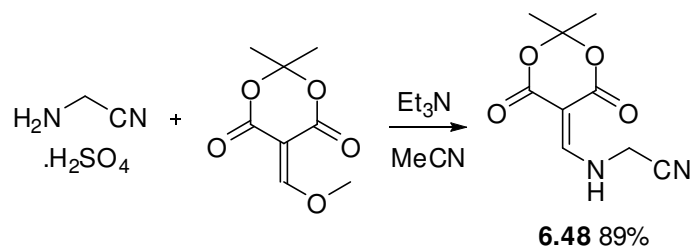


Scheme 6.22 Synthesis and pyrolysis of compound **6.47**

The likely reason for this is that the phenyl group cannot stabilise the intermediates and transition states sufficiently to allow the formation of the product. This then leads to side reactions, generating the complex mixtures observed.

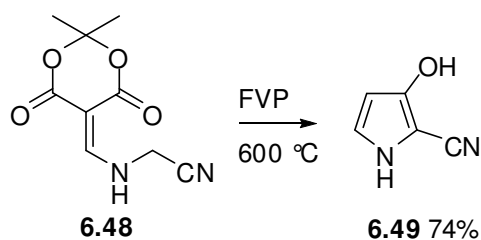
The nitrile group is another electron-withdrawing group that can potentially stabilise the intermediates required, by delocalisation of the charge. The pyrolysis precursor **6.48** was synthesised from 2-aminoacetonitrile sulfate and methoxymethylene

Meldrum's acid in 89% yield (Scheme 6.23)



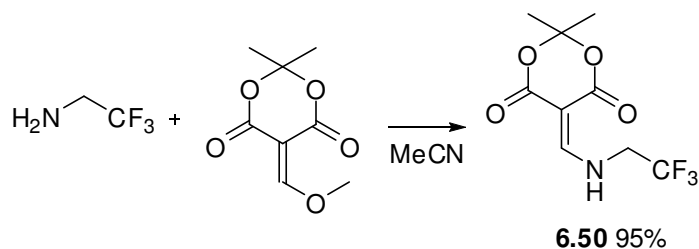
Scheme 6.23 Synthesis of compound **6.48**

Pyrolysis of compound **6.48** at 600 °C gave an off-white solid, the ^1H NMR spectrum and mass spectra of which were consistent with the formation of 3-hydroxy-2-cyanopyrrole **6.49** (Scheme 6.24).



Scheme 6.24 Pyrolysis of compound **6.48**

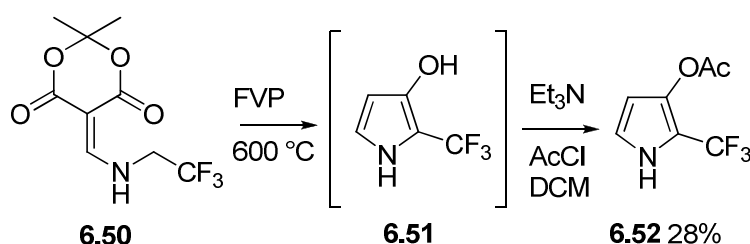
A 2-trifluoromethyl substituent was also used, because while it is an electron-withdrawing group it does so by inductive effects rather than resonance effects. The precursor **6.50** was synthesised in good yield from trifluoroethylamine and methoxymethylene Meldrum's acid (Scheme 6.25).



Scheme 6.25 Synthesis of compound **6.50**

Pyrolysis of compound **6.50** gave an orange oil, which showed the presence of the hydroxypyrrole as well as other impurities. Attempts to isolate the hydroxypyrrole

6.51 by column chromatography or distillation failed. Therefore the compound was taken as the crude pyrostate, dissolved in DCM and acetylated with acetyl chloride and triethylamine. This gave an orange oil, which could be distilled to give 3-acetoxy-2-trifluoromethylpyrrole **6.52** as a clear oil in 28% yield over 2 steps (Scheme 6.26)



Scheme 6.26 Synthesis of compound **6.52**

In summary, electron-withdrawing groups appear to be required for the hydroxypyrrole cyclisation to work, although electron-withdrawing groups that work *via* both inductive and resonance mechanisms have been shown to form hydroxypyrroles.

6.2.4 Tautomerism of Hydroxypyrroles

As previously stated, hydroxypyrroles can adopt two tautomers in solution, the 3-hydroxypyrrole and pyrrol-3(2*H*)-one forms. As a general rule, the pyrrolone tautomer is favoured in non-polar solvents (such as CDCl_3), while polar solvents (such as d_6 -DMSO) favour the hydroxypyrrole tautomer. However, compound **6.35** has only been observed in the hydroxypyrrole tautomer, presumably due to a hydrogen bonding interaction between the ester carbonyl and the hydroxyl hydrogen atom (Figure 6.5)

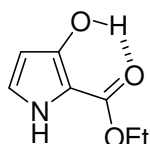
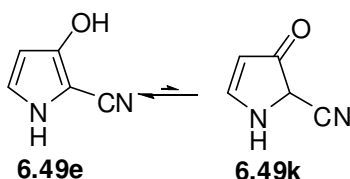


Figure 6.5

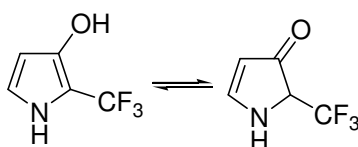
3-Hydroxy-2-cyanopyrrole **6.49** cannot form this hydrogen bond, but the electron-

withdrawing effect of the group may stabilise the hydroxypyrrole tautomer. From the ^1H NMR spectrum of compound **6.49**, the presence of 2 broad signals at $\delta_{\text{H}} = 11.23$ ppm and $\delta_{\text{H}} = 9.72$ ppm, which are due to the protons on the oxygen and nitrogen atoms, as well as the presence of two further protons at $\delta_{\text{H}} = 6.78$ ppm and $\delta_{\text{H}} = 5.65$ ppm show that the hydroxypyrrole tautomer **6.49e** is favoured over the pyrrolone tautomer **6.49k** (Scheme 6.27)



Scheme 6.27 Tautomerism of compound **6.49**

The ^1H NMR spectrum of the crude pyrostate of the 3-hydroxy-2-trifluoropyrrole **6.51** showed a number of impurities in the spectrum, but from the spectrum the presence of both tautomeric forms could be observed from the presence of doublet at around $\delta_{\text{H}} = 4.5$ ppm (due to the pyrrolone tautomer) and a pyrrole-like peak at $\delta_{\text{H}} = 6.5$ ppm. The implication of this result is that the inductive electron-withdrawing effect of the trifluoromethyl group is not strong enough to favour only the hydroxypyrrole tautomer, unlike cyano- and ester groups (Scheme 6.28).



Scheme 6.28 Tautomerism of compound **6.51**

For the 2,2-disubstituted compounds **6.43** – **6.45**, the hydroxypyrrole tautomer cannot exist and so only the pyrrolone tautomer is observed in the ^1H NMR spectrum (Figure 6.6)

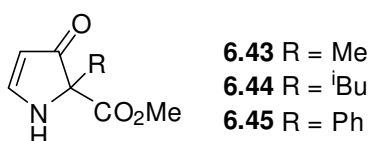
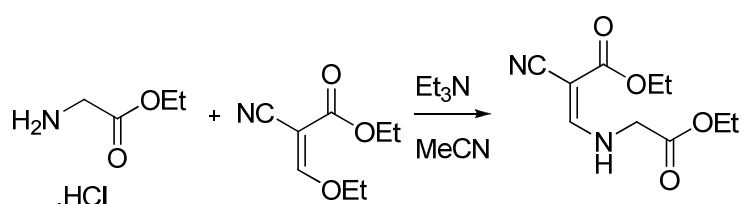


Figure 6.6

6.2.5 Alternative Ketene Generators

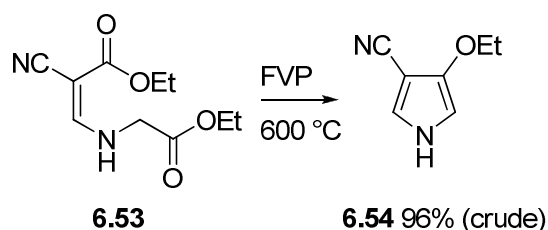
Alternative ketene generators, such as acrylate esters, generate imidoalkenes directly. Therefore it would be expected that ketenes derived from these molecules should not give hydroxypyrroles in the same way as the Meldrum's acid derivatives.

The precursor **6.53** was synthesised from glycine ethyl ester hydrochloride and ethyl ethoxymethylenecyanoacetate, using the same conditions as the methylene Meldrum's acid example in 94% yield (Scheme 6.29).



Scheme 6.29 Synthesis of compound **6.53**

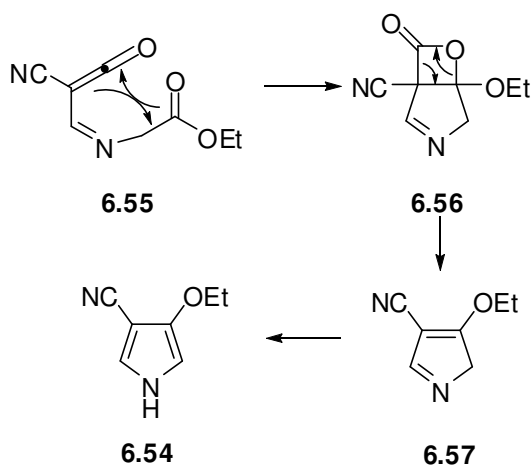
Pyrolysis of compound **6.53** gave a dark brown oil, the NMR of which showed the presence of two pyrrole peaks and an ethyl group. The mass spectrum of the compound showed a molecular ion of $m/z = 135$. This is 90 Da lower than the starting material and assuming the mechanism proceeds with loss of ethanol (see chapter 2) in the initial stages leaves the remaining mass to be 44 Da, the weight of carbon dioxide. One possible structure is 3-ethoxy-4-cyanopyrrole **6.54** (Scheme 6.30).



Scheme 6.30 Pyrolysis of compound **6.53**

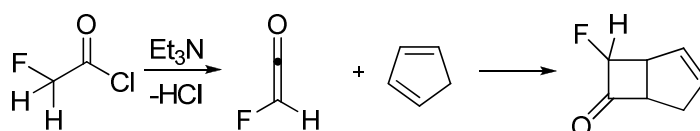
The mechanism for the formation of compound **6.54** is shown in scheme 6.31. The initial loss of ethanol gives the imidoalkene **6.55**. A [2+2] cycloaddition of the ketene with the carbonyl of the ester gives the 5,4 ring system **6.56**, which can undergo

decarboxylation to give the 2*H* pyrrole **6.57**. This can then tautomerise to the product **6.54**.



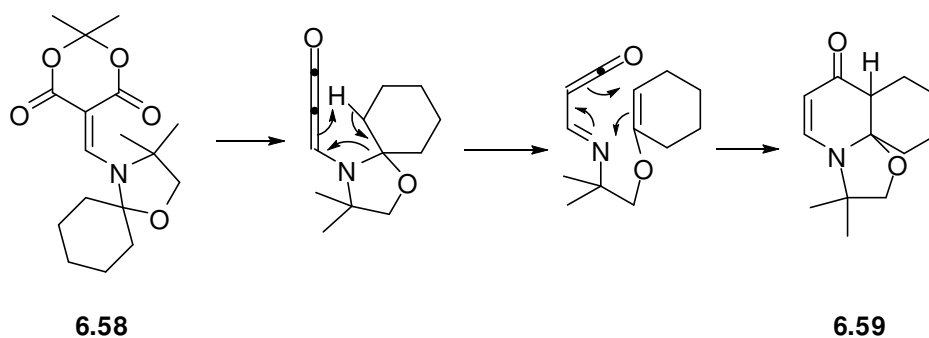
Scheme 6.31 Mechanism for the formation of compound **6.54**

[2+2] Cycloadditions of ketenes are well known, generating cyclobutanones.¹³⁵ For example, reaction of fluoroketene with cyclopentadiene gives the 5,4 ring system (Scheme **6.32**).



Scheme 6.32 Reaction of fluoroketene with cyclopentadiene

Pyrolysis of a related system **6.58** was observed to generate a ketene which undergoes a [4+2] cycloaddition to generate the tricyclic compound **6.59** (Scheme **6.33**).

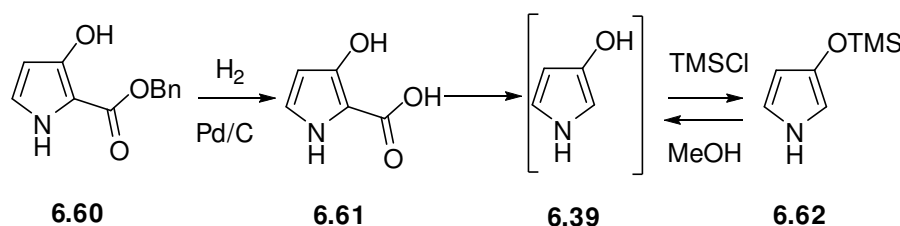


Scheme 6.33 Pyrolysis of compound **6.58**

This route gives the alkoxyrrole **6.54** in a reasonable crude yield, but there were problems in purification of the compound. However it allows access to a compound that would be difficult to synthesis by other methodology. Preliminary investigations into other precursors of this type failed to yield any results.

6.2.6 Synthesis of 3-Hydroxypyrrole by Flash Vacuum Pyrolysis

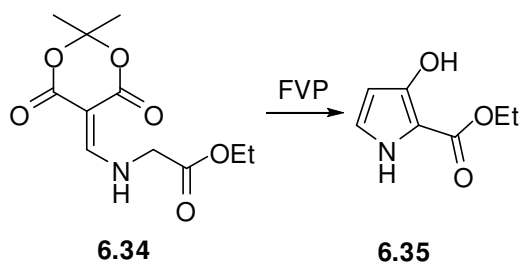
3-Hydroxypyrrole **6.39** is a rare compound, subject to theoretical discussions but having only been previously synthesised once in the literature.¹³⁶ Capon and Kwok synthesised 3-hydroxypyrrole **6.39** by hydrogenolysis of benzyl 3-hydroxypyrrole-2-carboxylate **6.60** in solution to give the 3-hydroxypyrrole-2-carboxylic acid **6.61**. This then undergoes *in situ* decarboxylation to give 3-hydroxypyrrole **6.39**, which was protected as its trimethylsilyl ether **6.62** and deprotected with methanol when required (Scheme 6.34).



Scheme 6.34 Capon's route to 3-hydroxypyrrole **6.39**

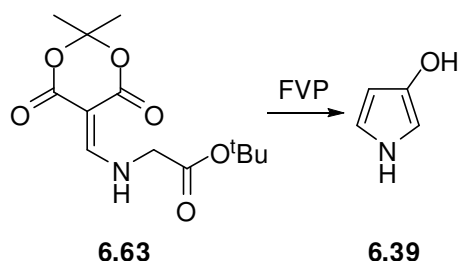
During this synthesis, it was remarked upon that 3-hydroxypyrrole was “an unstable oil, which resinified very rapidly”.¹³⁶ From the benzyl ester **6.60** (which requires 5 steps to synthesise), 2 steps were required to isolate the silyl compound **6.62**, with yields “greater than 90%” reported for a range of related silyl compounds but no actual yield given. No yield for the synthesis of 3-hydroxypyrrole **6.39** was reported, some spectral properties were reported and no further reactions were carried out on the compound.

Previously, the synthesis of ethyl 3-hydroxypyrrole-2-carboxylate **6.35** was shown to proceed from the methylene Meldrum's acid derivative of glycine ethyl ester **6.34** in good yield (Scheme 6.35).



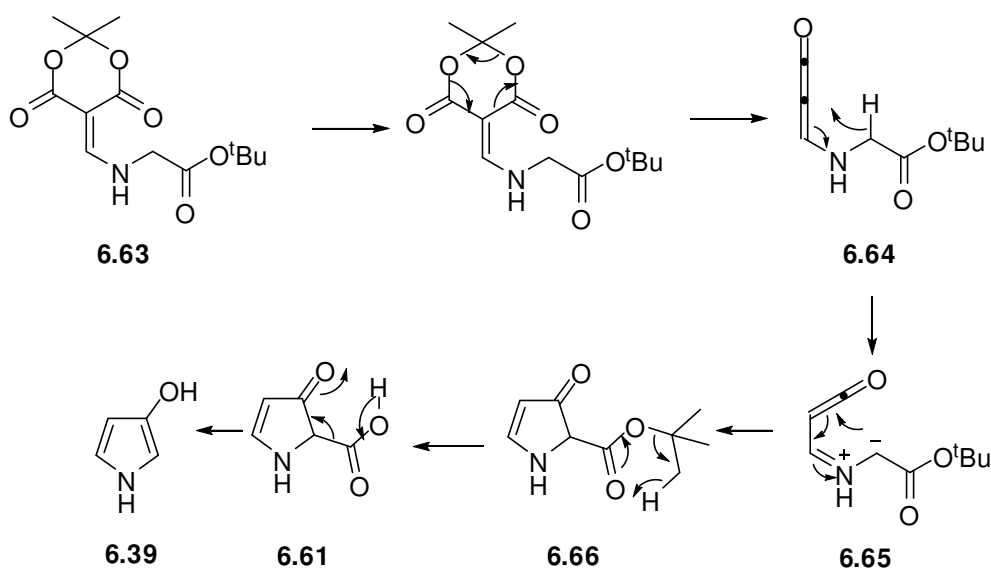
Scheme 6.35 Synthesis of compound **6.35**

From previous work (chapter 1 and previous work⁷), it has been shown that flash vacuum pyrolysis of esters with a β -H atom can lead to loss of the alkyl group of the ester to give the free acid. Pyrolysis of **6.34** with an increased the furnace temperature from 600 °C to 850 °C lead to the formation of a dark oil. The ¹H NMR spectrum of the crude compound in *d*₆-DMSO showed signs of decomposition, but also three pyrrole-like peaks. These peaks were most likely due to the formation of 3-hydroxypyrrole, but the higher furnace temperature was causing it to decompose in the reaction. *tert*-Butyl esters have been shown to eliminate at much lower furnace temperatures than ethyl groups (see chapter 1), which would hopefully minimise the amount of decomposition. Therefore using the *tert*-butyl precursor **6.63**, it should be possible to generate 3-hydroxypyrrole **6.39** directly and more cleanly than with the ethyl ester (Scheme **6.36**).



Scheme 6.36 Proposed pyrolysis of compound **6.63**

Compound **6.63** was synthesised from glycine *tert*-butyl ester and methoxymethylene Meldrum's acid in 89% yield. Pyrolysis of compound **6.63** at 600 °C gave 3-hydroxypyrrole as an orange oil. Due to the difficulty in isolating 3-hydroxypyrrole, the yield was recorded based on an NMR internal standard (cyclohexane), which was around 55%. The mechanism for the formation of 3-hydroxypyrrole is given in Scheme **6.37** (below).



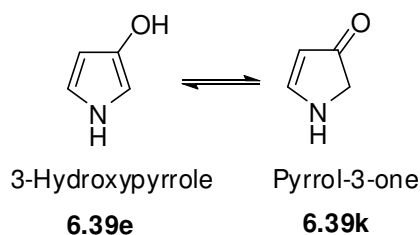
Scheme 6.37 Mechanism for the formation of compound **6.39**

As with the previous examples, the Meldrum's acid component undergoes loss of acetone and CO₂ to give the methyleneketene **6.64**. This then undergoes a 1,4 hydrogen shift to generate the azomethine ylide **6.65**, which can undergo electrocyclic closure to give the hydroxypyrrole **6.66**. The *tert*-butyl group can undergo a thermal loss of isobutene to give the free acid **6.61**, which then undergoes decarboxylation to give 3-hydroxypyrrole **6.39**.

The advantage to this route to 3-hydroxypyrrole is that since it is formed in the gas-phase, it avoids the problems of decomposition in solution and during isolation. It is a two step synthesis in an overall yield of *ca.* 49% yield from readily available starting materials.

3.2.7 Tautomerism of 3-Hydroxypyrrole

3-Hydroxypyrrole can exist as two possible tautomers, the "hydroxypyrrole" **6.39e** and "pyrrolone" **6.39k** tautomers (Scheme 6.38).



Scheme 6.38 Tautomerism of 3-hydroxypyrrole **6.39**

Previous work on 1-substituted 3-hydroxypyrroles has shown that the ratio of tautomers changes with the solvent.¹³⁷ Chloroform, for example, shows mainly the keto form, while DMSO shows the enol form to be the major tautomer. This is general for most of the 1-substituted 3-hydroxypyrroles, with one or two exceptions.

3-Hydroxypyrrole proved insoluble in deuteriated chloroform and no spectra were obtained of the compound.

In d_6 -DMSO, a major tautomer can be clearly observed with a small trace amount of the other tautomer (Figure 6.7).

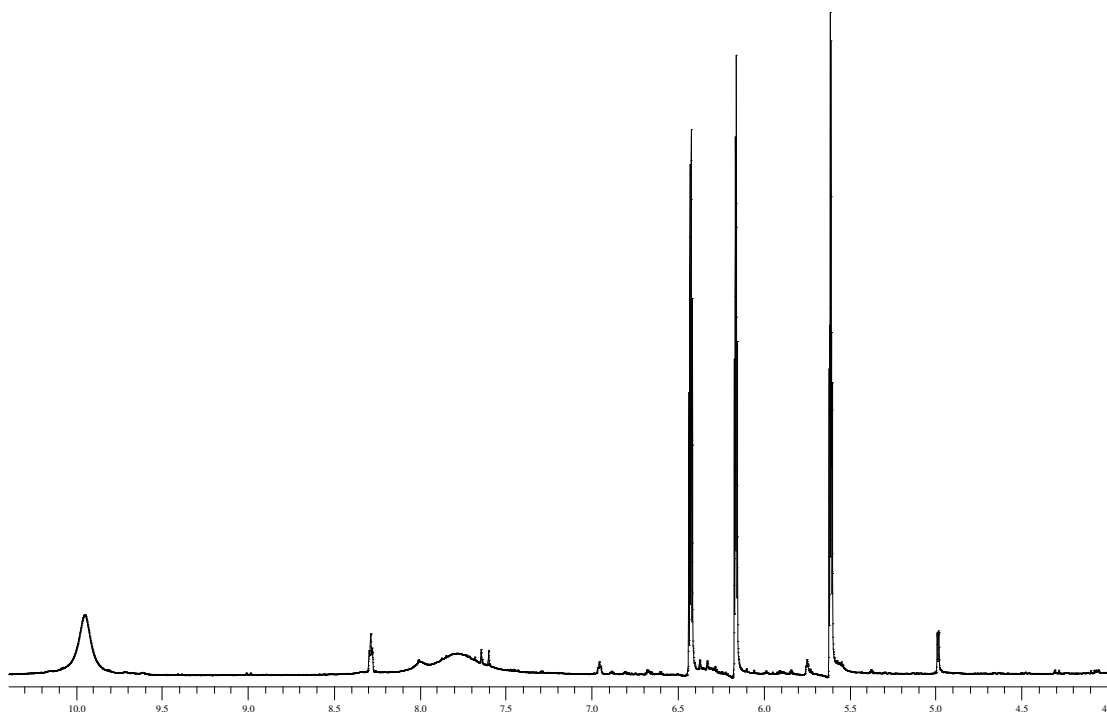


Figure 6.7 d_6 -DMSO ^1H NMR spectrum of compound **6.39**

Three pyrrole-like peaks can clearly be seen in figure 6.7, along with two broad

signals corresponding to the NH and OH protons. The minor isomer, 1*H*-pyrrol-3(2*H*)-one shows two pyrrole peaks at $\delta_H = 8.3$ ppm and $\delta_H = 5.0$ ppm, and a two proton signal at $\delta_H = 3.7$ ppm. The ^{13}C spectrum of the major isomer shows a quaternary carbon signal at $\delta_C = 143$ ppm, typical of the enol tautomer **6.39e**.

Obtaining NMR data in D_2O proved problematic due to rapid deuterium exchange of the 2-position of the molecule. NMR data obtained from H_2O with a small amount of D_2O added for deuterium locking purposes proved successful and with water suppression enabled, the spectrum shown below was obtained (Figure **6.8**).

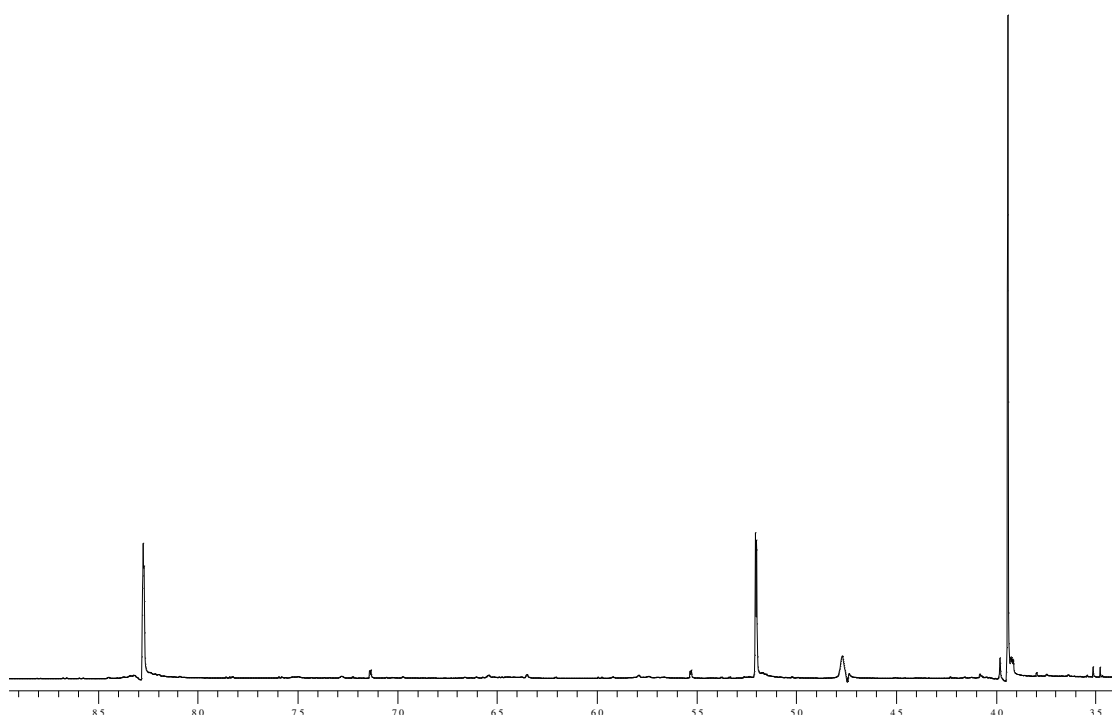


Figure 6.8 $\text{H}_2\text{O}/\text{D}_2\text{O}$ ^1H NMR spectrum of compound **6.39**

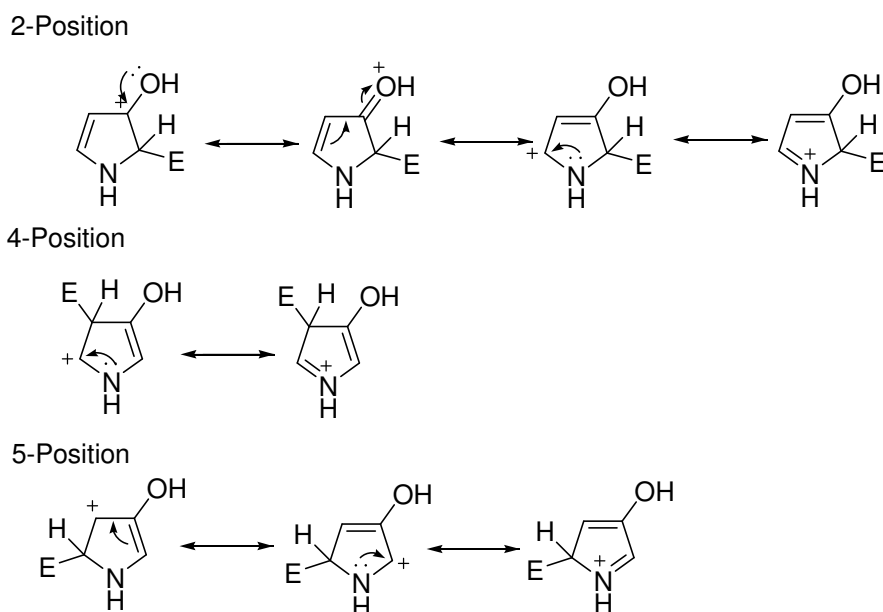
From figure **6.8**, two widely spaced protons can be seen at $\delta_H = 8.3$ ppm and $\delta_H = 5.2$ ppm and a two proton signal at $\delta_H = 3.8$ ppm. This clearly indicates that the major isomer in water is the keto tautomer **6.39k**, and none of the enol tautomer is visible in the spectrum. In pyrrol-3-ones, the 4-position in the keto tautomer is electron-rich and is typically observed at 4.8 – 5.2 ppm.¹³⁷ The 5-position is electron-deficient and is observed at 7.7 – 8.0 ppm.¹³⁷ The two protons in figure 6.8 can therefore be assigned to the 4-position at $\delta_H = 5.2$ ppm and the 5-position at $\delta_H = 8.3$ ppm. The two proton peak at $\delta_H = 3.8$ ppm is the two protons in the 2-position. This is further

confirmed in the ^{13}C spectrum, with the carbon at C3 resonating at $\delta_{\text{C}} = 204$ ppm in comparison with the enol tautomer, which resonates at $\delta_{\text{C}} = 143$ ppm in d_6 -DMSO.

In all solvents, prolonged exposure to air at room temperature lead to the solution changing from orange-brown to a deep black colour, along with the formation of an insoluble black solid.

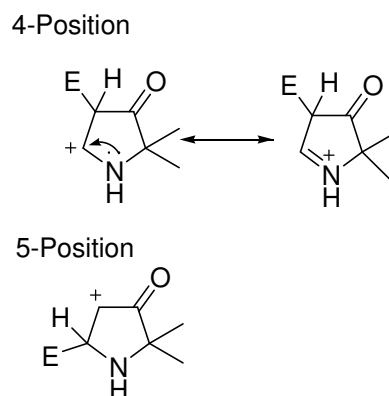
6.2.8 Reactions of 3-Hydroxypyrrole

Pyrrole itself is highly reactive towards electrophiles and previous work on 3-hydroxypyrroles has shown them to even more reactive. The hydroxypyrrole tautomer is reactive in the 2 position mainly, with the 5-position in the next most reactive position (Scheme 6.39).



Scheme 6.39 Resonance structures for the intermediates for electrophilic substitution reactions of 3-hydroxypyrrole 6.39

However, due to the possibility of keto-enol tautomerisation, the reactivity is more complicated. For 2,2-disubstituted pyrrolones, the electrophilic substitution reactions occur in the 4-position, consistent with the number of possible resonance structures (Scheme 6.40)

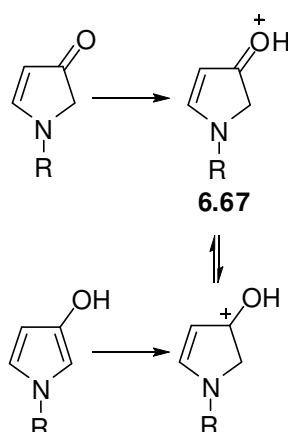


Scheme 6.40 Resonance structures for the intermediates for electrophilic substitution reactions of disubstituted pyrrolones

3-Hydroxypyrrole **6.39** would be expected to be highly reactive towards electrophiles, mainly reacting in the 2-position.

6.2.8.1 Protonation in TFA/*d*-TFA

Previous work on *N*-substituted 3-hydroxypyrroles has shown that protonation occurs on the oxygen atom giving the *O*-protonated species **6.67** in TFA.¹³⁸ Large changes in chemical shifts were observed both ¹H and ¹³C NMR spectra of the compounds, due to the protonation of the compound (Scheme **6.41**)



Scheme 6.41 Protonation of *N*-substituted 3-hydroxypyrroles

In *d*-TFA, deuterium exchange of the *N*-substituted derivatives occurs at the 2- and 4-positions only. The half lives for the exchanges were found to be fast, at <1 min for the 4-position and around 6 min for the 2-position. No exchange was observed in the

5-position, even after several days.

Dissolution of 3-hydroxypyrrole in TFA lead to the formation of a deep red solution and the ^1H and ^{13}C NMR spectra were recorded. The ^1H NMR spectroscopic data for the protonated species are shown in table **6.2** below, with *N*-tert-butyl and *N*-phenyl 3-hydroxypyrroles included for comparison.

R	$\delta_{\text{H}2}$	$\delta_{\text{H}4}$	$\delta_{\text{H}5}$	$^3J_{4,5}$
H	5.02 (+0.99)	6.34 (+1.34)	8.92 (+0.55)	2.0 (-0.9)
$^t\text{Bu}^{136}$	4.81 (+0.86)	5.99 (+0.90)	8.62 (+0.69)	2.2 (-1.3)
Ph^{136}	5.26 (+1.16)	6.26 (+1.20)	8.93 (+0.53)	2.3 (-1.1)

Table 6.2 ^1H NMR data for 3-hydroxypyrroles in TFA (Chemical shift changes relative to d_6 -DMSO shown in brackets)

The corresponding ^{13}C NMR data is shown below (table **6.3**).

R	$\delta_{\text{C}2}$	$\delta_{\text{C}3}$	$\delta_{\text{C}4}$	$\delta_{\text{C}5}$
H	54.83 (+0.72)	189.23 (-14.98)	100.17 (-0.94)	173.17 (+2.34)
$^t\text{Bu}^{136}$	56.51 (+3.32)	186.84 (-11.87)	100.86 (+1.73)	170.04 (+7.46)
Ph^{136}	59.06 (+3.41)	189.52 (-10.24)	102.35 (-1.46)	168.89 (+10.58)

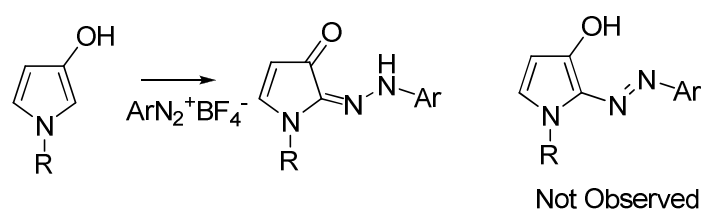
Table 6.3 ^{13}C NMR data for 3-hydroxypyrroles in TFA (Chemical shift changes relative to d_6 -DMSO shown in brackets)

Chemical shift changes of similar magnitudes were observed in the ^1H NMR spectrum of 3-hydroxypyrrole and the *N*-substituted analogues. Similar chemical shift changes were observed in the C3 carbon signal. No decomposition was observed in the TFA sample of 3-hydroxypyrrole over the course of several hours.

In *d*-TFA, after the time taken to prepare the sample and run the spectrum (*ca.* 5 min), both the protons in the 2- and 4- positions had fully exchanged and were not observed in the ^1H NMR spectrum. This rate of reaction is similar to that observed in the case of *N*-substituted hydroxypyrroles.

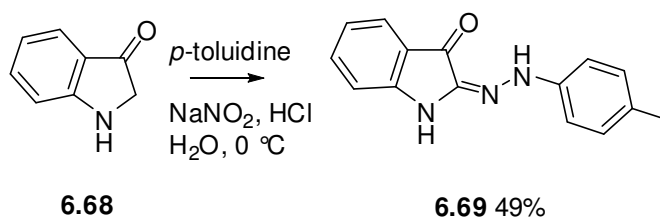
6.2.8.2 Reaction with Diazonium Salts

N-Substituted 3-hydroxypyrroles have been shown to react with benzenediazonium tetrafluoroborate to give the 2-hydrazono-3-pyrrolone product rather than the 2-azo-3-hydroxypyrrole tautomer¹³⁹ (Scheme 6.42)



Scheme 6.42 Reaction of *N*-substituted 3-hydroxypyrroles with diazonium salts

Indoxyl **6.68** reacts with diazonium salts, this time generated *in situ*, in a similar fashion, to give the hydrazone tautomer of the coupled product **6.69**, isolated in 49% yield²⁸ (Scheme 6.43).



Scheme 6.43 Reaction of Indoxyl **6.68** with diazonium salts

Addition of *p*-tolylidiazonium tetrafluoroborate, synthesised as described in chapter 4, to the solution of 3-hydroxypyrrole **6.39** in DMF gave immediate colour change from orange to deep red, typical of the azo-coupling reaction. Upon work up and purification by column chromatography, a red solid **6.70** was obtained in 56% in the 2 steps from the glycine precursor **6.63**.

The tautomerism of the molecule was also of interest, as the previous products of azo coupling of 1-substituted 3-hydroxypyrroles were shown to be in the pyrrolone tautomer, with the azo group in the hydrazone tautomer. The ^1H NMR spectrum of the compound **6.70** is shown below (Figure 6.9)

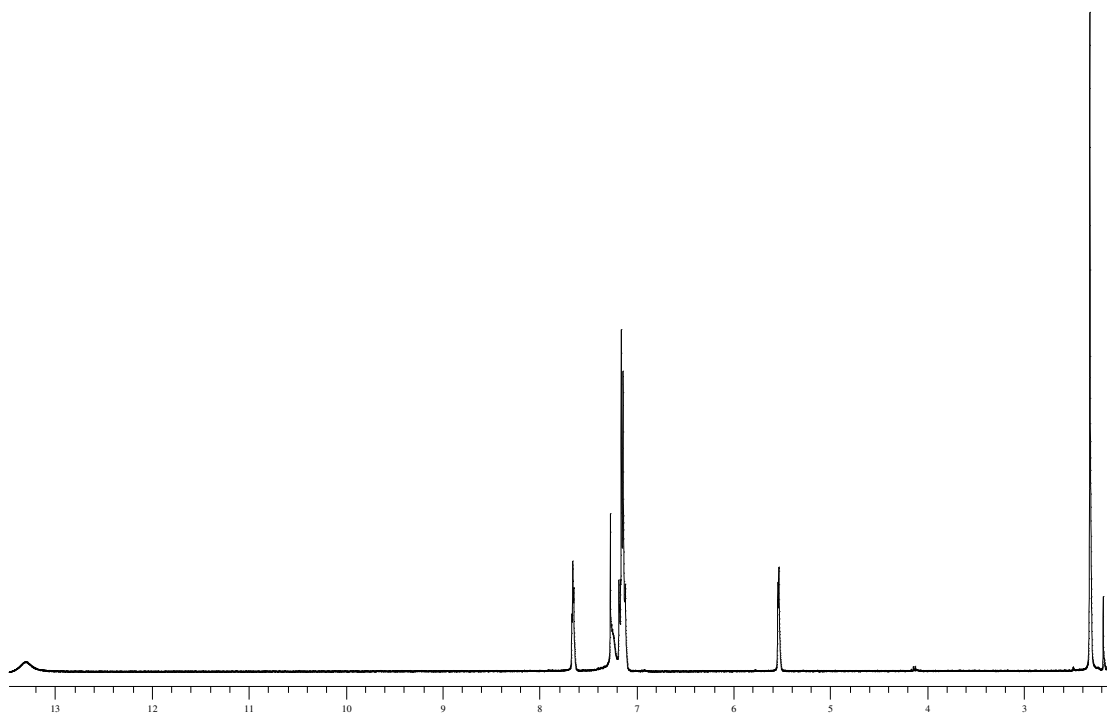


Figure 6.9 ^1H NMR spectrum (CDCl_3) of compound **6.70**

From figure 6.9, the two protons at $\delta_H = 7.6$ ppm and $\delta_H = 5.5$ ppm correspond to the two protons from the pyrrole ring. The chemical shifts of these two protons are typical of the pyrrolone tautomer, along with the hydrazone NH at $\delta_H = 13.2$ ppm. This is confirmed in the ^{13}C NMR spectrum, which shows a quaternary carbon signal at $\delta_C = 178$ ppm, typical of the pyrrolone tautomer. This behaviour is consistent with the products of previous azo-coupling reactions of 3-hydroxypyrroles.

The UV-Vis spectrum of 2-hydrazonopyrrol-3-ones has been reported to feature 3 peaks in a methanol solution.¹³⁹ In particular, compound **6.71** (figure 6.10) shows peaks at $\lambda_{\text{max}}/\text{nm}$ of 469, 376 and 265. In comparison compound **6.70** features peaks at $\lambda_{\text{max}}/\text{nm}$ of 456, 373 and 260. These values compare favourably and support the hydrazone structure of compound **6.70**.

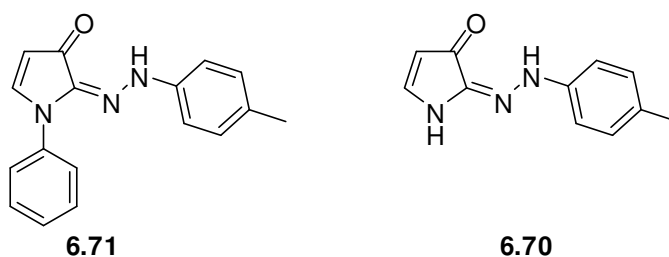
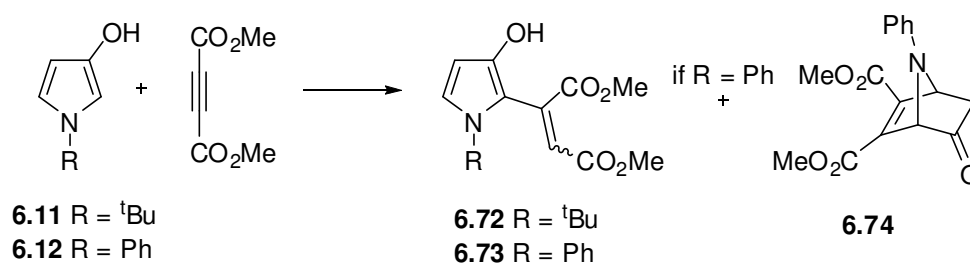


Figure 6.10 Structures of compound **6.70** and **6.71**

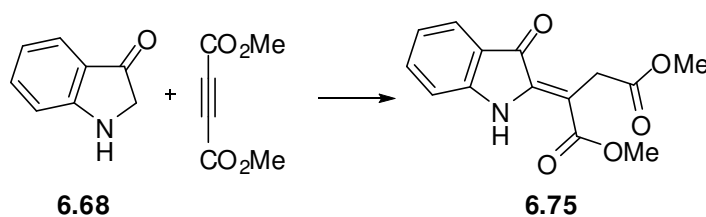
6.2.8.3 Reaction with Dimethyl Acetylenedicarboxylate (DMAD)

Dimethyl acetylenedicarboxylate has been previously shown to react with 1-substituted 3-hydroxypyrroles. The reaction mode of the compound was different depending on the group in the 1-position.¹⁴⁰ 1-*tert*-Butyl-3-hydroxypyrrole **6.11** reacts with DMAD in a Michael fashion to give the compound **6.72**, while 1-phenyl-3-hydroxypyrrole **6.12** undergoes cycloaddition to give the azanorbornene **6.74** as well as the Michael product **6.73** (Scheme 6.44)



Scheme 6.44 Reaction of compounds **6.11** and **6.12**

Indoxyl **6.68** reacts with dimethyl acetylenedicarboxylate to give the Michael addition product **6.75** only.²⁸ However the product was found to be in the keto form, with the double bond formed at the ring (Scheme 6.45)



Scheme 6.45 Reaction of Indoxyl **6.68** with DMAD

This structure was confirmed by X-ray crystallography, showing the NH of the indoxyl hydrogen bonding to the carbonyl of the ester. With the 1-substituted 3-hydroxypyrroles, this cannot occur and the products adopt the hydroxypyrrole tautomer instead.

Addition of dimethyl acetylenedicarboxylate to a solution of 3-hydroxypyrrole in DMF lead to the formation of a brown solid. Purification by column chromatography gave a red solid, isolated in 41% yield over the 2 steps. Only 1 product was isolated from the reaction mixture and its ^1H NMR spectrum is shown below (Figure 6.11)

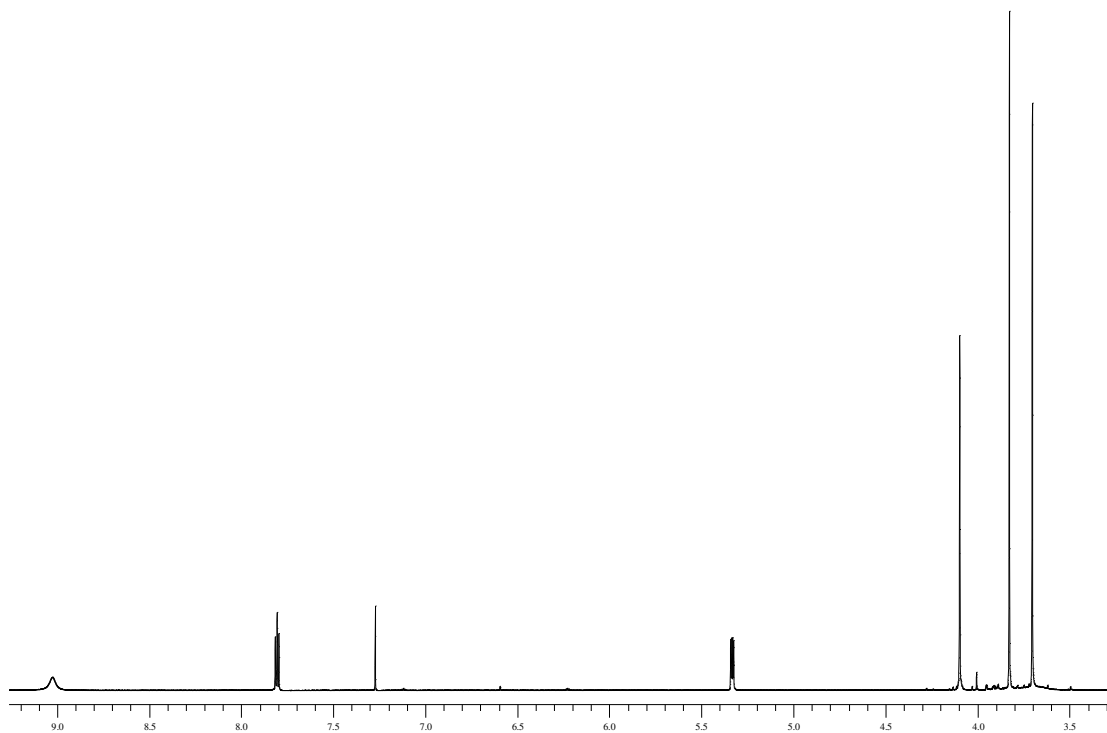


Figure 6.11 ^1H NMR Spectrum (CDCl_3) of compound **6.76**

From figure 6.11, the typical pyrrolone peaks at $\delta_H = 7.8$ ppm and $\delta_H = 5.3$ ppm are present, showing that the compound has adopted the pyrrolone tautomer, ruling out the cycloaddition product. Also present is a two proton singlet $\delta_H = 4.1$ ppm, indicating that the double bond has adopted the succinate form over the acrylate, similarly as was observed with indoxyl (Figure 6.12).

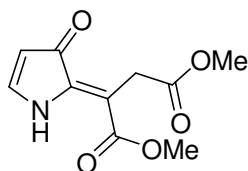
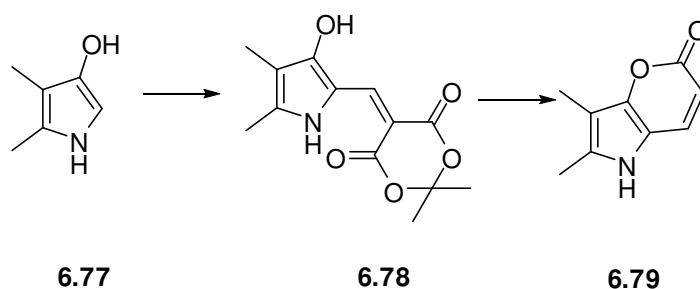


Figure 6.12 Structure of compound **6.76**

As with indoxyl **6.68**, the likely explanation for the tautomerisation of the molecule is due to hydrogen bonding between the NH of the pyrrolone ring and the carbonyl of the ester group.

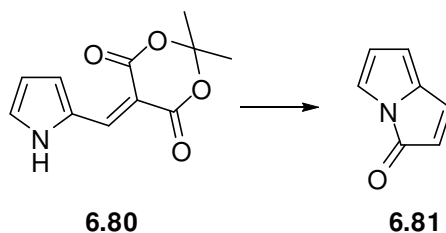
6.2.8.4 Reaction with Methoxymethylene Meldrum's Acid

Methoxymethylene Meldrum's acid is a weak electrophile. Pyrrole requires a reaction time of several days and reacts in the 2-position. 4,5-Dimethyl-3-hydroxypyrrole **6.77** was shown to react faster to give the 2-substituted product **6.78**. Pyrolysis of this generates the pyrone **6.79** (Scheme **6.46**).



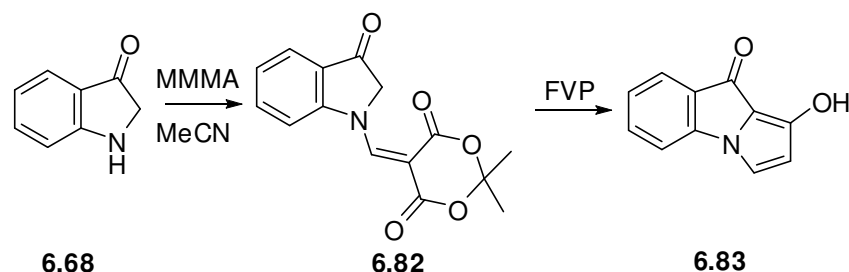
Scheme 6.46 Synthesis and pyrolysis of compound **6.78**

This is in contrast with the pyrolysis of 2-methylene Meldrum's acid derivatives of pyrroles **6.80**, which typically undergo a different reaction to give pyrrolizin-3-ones **6.81** (Scheme **6.47**)



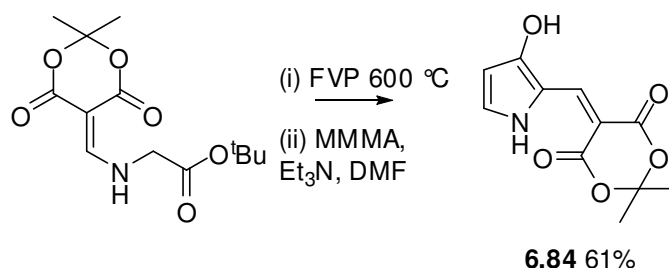
Scheme 6.47 Pyrolysis of compound **6.80**

Indoxyl **6.68** was shown to react with methoxymethylene Meldrum's acid in the 1-position to give *N*-methylene Meldrum's product **6.82**.²⁸ Pyrolysis of this compound gave a novel heterocyclic system **6.83** (Scheme 6.48).



Scheme 6.48 Synthesis and pyrolysis of compound **6.82**

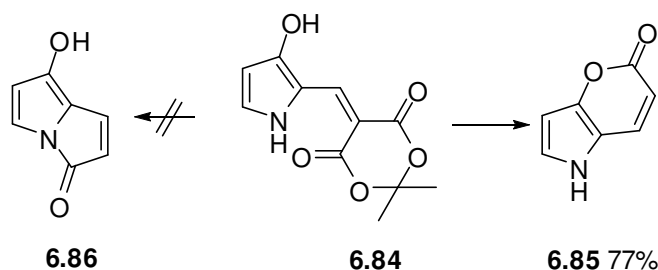
Attempts to use acetonitrile, the typical solvent for these reactions, proved problematic due to the poor solubility of 3-hydroxypyrrole. The use of DMF increased the solubility of the starting material, but upon work-up a complex mixture of products was obtained. Addition of triethylamine to the DMF solution gave a single product upon work-up. This was identified as the 2-substituted product from the ¹H NMR spectrum, which showed the presence of two broad signals and two pyrrole-type peaks (Scheme 6.49)



Scheme 6.49 Synthesis of compound **6.84**

As previously mentioned, pyrolysis of these Meldrum's compounds tends to form pyrones by cyclisation onto the hydroxyl group, rather formation of the pyrrolizinone that typical for 2-methylene Meldrum's substituted pyrroles. Pyrolysis of compound **6.84** gave a brown solid, isolated in 77% yield. The ¹H NMR spectrum of the compound showed the presence of two pyrrole peaks at $\delta_H = 7.05$ and $\delta_H = 6.23$ ppm along with two doublets at $\delta_H = 7.58$ and $\delta_H = 6.05$ ppm. The coupling constants of

the two doublets are 9.5 Hz, consistent with the pyrone structure **6.85** rather than the pyrrolizinone **6.86** (Scheme 6.50), which would have a much smaller coupling constant.

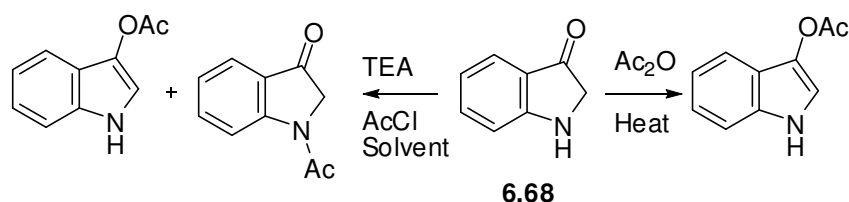


Scheme 6.50 Pyrolysis of compound **6.84**

6.2.8.5 Acetylation of 3-Hydroxypyrrole

Acetylation of 3-hydroxypyrroles has been previously reported, for derivatives substituted or unsubstituted in the 1- position. In most cases *O*-acetylation (and *N*-acetylation for *N*-unsubstituted examples) was observed, but a number of examples also show *C*-acetylation under appropriate conditions (such as acetic anhydride/perchloric acid).¹²⁵

Indoxyl **6.68**, the benzo analogue of 3-hydroxypyrrole, acetylates in different positions dependent on the conditions used.²⁸ Heating indoxyl in neat acetic anhydride gave *O*-acetylated product in 91% yield. Using acetyl chloride and triethylamine, varying the solvent changed the ratio of *O* to *N* acetylation (Scheme 6.51)

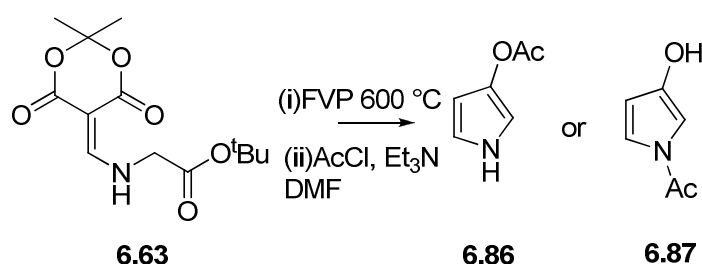


Scheme 6.51 Acetylation of Indoxyl **6.68**

Heating 3-hydroxypyrrole in neat acetic anhydride for 5 minutes, lead to the formation of a dark orange oil, after removal of the excess acetic anhydride. The ¹H

NMR spectrum of the crude material showed a complex mixture of products, indicating that both *N*- and *O*- acetylated products **6.87** and **6.86** had been formed along with multiple acetylated products.

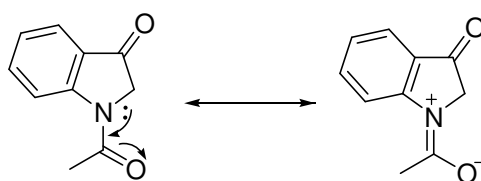
Treatment of 3-hydroxypyrrole with acetyl chloride and triethylamine in DMF led to the formation of a dark brown oil. However the ^1H NMR spectrum of the crude material showed the main component was a single product. Purification by Kugelrohr distillation lead to the formation of an orange oil in 49% yield from the Meldrum's acid precursor (Scheme **6.52**)



Scheme 6.52 Acetylation of 3-hydroxypyrrole

The orange oil darkened over time, hinting that the compound is sensitive to oxidation at room temperature. Storage in the freezer showed no change in colour over time, showing that the compound was apparently stable when stored at -20 C.

The ^1H NMR of the product showed the presence of 3 pyrrole-like protons and a broad singlet. Previous work on indoxyl has shown that the *N*-acetylated product assumes the keto tautomer. This is due to the location of the lone pair of the nitrogen atom, which in the keto tautomer can delocalise into the carbonyl of the acetyl group giving extra stabilisation. In the enol tautomer, the lone pair is part of the π system and cannot delocalise into the carbonyl (Scheme **6.53**)



Scheme 6.53 Delocalisation in 1-acetylindole

The lack of a CH₂ signal in the ¹H NMR spectrum of the acetylated product hints at the product being *O* rather than *N*-acetylated.

Comparison of the chemical shifts of the acetyl groups in compounds **6.88** – **6.90** also show the difference between *N* and *O*-acetylation (Figure **6.13**).¹⁴¹

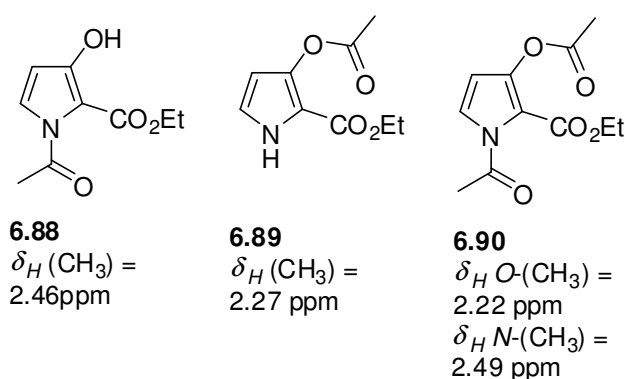


Figure 6.13 Chemical shifts of compounds **6.88** – **6.90**

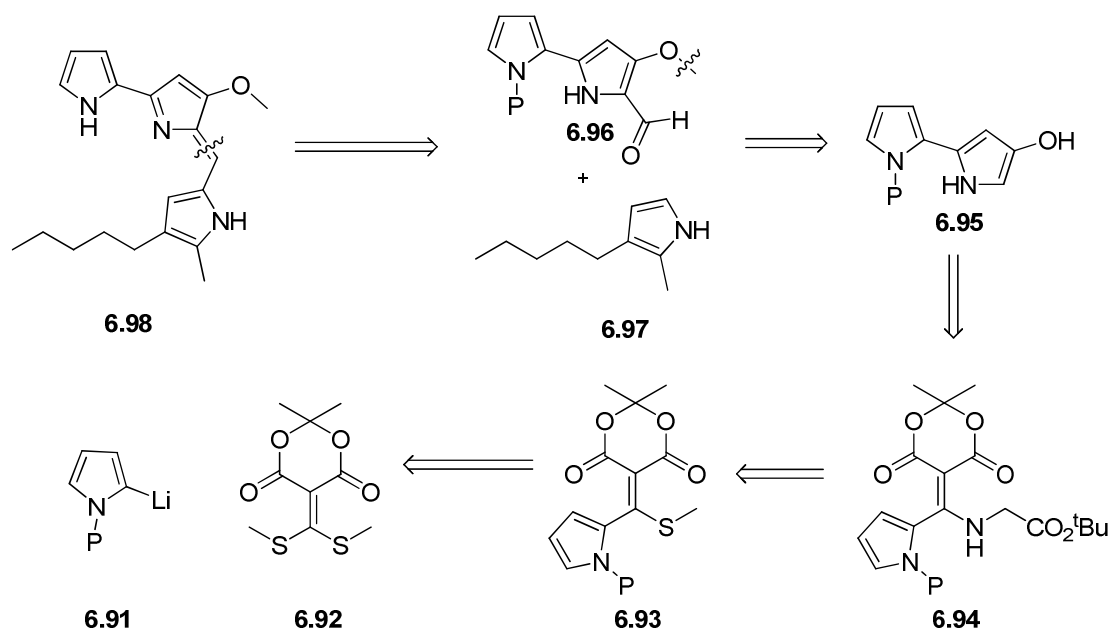
From figure **6.13**, we can see that the methyl of the acetyl group in the *N*-acetyl compound is approximately 0.2 ppm higher than the *O*-acetyl compound, and this is reflected in the diacetyl compound **6.90**. The ¹H NMR spectrum of the acetylated product of 3-hydroxypyrrole shows the methyl group to be at $\delta_H = 2.24\text{ ppm}$, which is consistent with *O*-acetylation product **6.86**.

Conclusion

Using electron-withdrawing groups, it has been possible to divert N-H aminomethyleneketenes away from their standard reactivity to give 3-hydroxypyrroles and pyrrol-3-ones in good yields. This methodology has also been extended to give 3-hydroxypyrrole **6.39**, in 2 steps from commercially available starting materials, and the reactions of 3-hydroxypyrrole have been explored.

This strategy may also be applied to a potential total synthesis of Prodigiosin. In previous attempts to synthesis the alkoxy core of Prodigiosin, the *N*-unsubstituted pyrrole proved difficult to synthesise and required a number of steps to obtain. This work potentially allows for that compound to be synthesised in 2 – 3 steps relatively

quickly. A potential retrosynthesis is shown below (Scheme 6.54).



P = Protecting Group

Scheme 6.54 Potential retrosynthesis of prodigiosin

A potential synthesis of prodigiosin **6.98** could begin with the controlled organometallic addition of the protected lithiopyrrole **6.91** to the bithiomethyl compound **6.92**. Addition of glycine *tert*-butyl ester to compound **6.93** gives the pyrolysis precursor **6.94**, which upon pyrolysis gives the linked dipyrrole **6.95**. *O*-Alkylation of the hydroxyl group and formylation gives the methoxy compound **6.96**, which could be condensed with pyrrole **6.97** to give prodigiosin **6.98**.

Experimental

General Methods

Abbreviations are contained in the preamble at the start of this thesis. The general experimental data (instrumental details etc.) are contained in the experimental section of chapter 1.

Method A – Synthesis of Meldrum's acid derivatives from amine salts

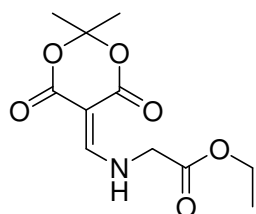
Triethylamine (0.28 cm³ per mmol) was added to a solution of the amine salt (1 equivalent) in acetonitrile (15 cm³ per mmol). Methoxymethylene Meldrum's acid (1 equivalent) was added and the solution stirred for 2.5 h at room temperature. The solvent was removed, the residue dissolved in DCM and washed with HCl (2M). The organic layer was dried over MgSO₄ and the solvent removed to give the product.

Method B – Synthesis of Meldrum's acid derivatives from the free base

To a solution of the amine (1 equivalent) dissolved in the minimal amount of acetonitrile, was added methoxymethylene Meldrum's acid (1 equivalent). The mixture was allowed to stand for 15 min and the solvent removed to give the product.

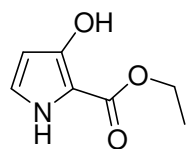
Ethyl [(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-acetate

6.34



Using general method A, glycine ethyl ester hydrochloride (1.396 g, 10 mmol) gave ethyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-acetate **6.34** as a yellow solid (1.965 g, 77%); mp 125 – 126 °C (from ethanol); (Found C, 51.4; H, 5.85; N, 5.45. C₁₁H₁₅NO₆ requires C, 51.35; H, 5.85; N, 5.45.); δ_H 9.65 (1H, br, s), 8.09 (1H, d, 3J 14.5), 4.25 (2H, q, 3J 7.2), 4.19 (2H, d, 3J 6.1), 1.69 (6H, s) and 1.30 (3H, t, 3J 7.2); δ_C 167.35 (quat), 165.23 (quat), 163.63 (quat), 160.21, 104.52 (quat), 86.06 (quat), 62.34 (CH₂), 50.24 (CH₂), 26.90 (2CH₃) and 14.04 (CH₃); m/z 257 (M⁺, 49%), 200 (55), 155 (61) and 126 (100).

Ethyl 3-Hydroxypyrrole-2-carboxylate **6.35**

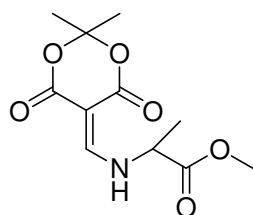


Pyrolysis of ethyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-acetate **6.34** (w 1.09 g, T_f 600 °C, T_i 200 °C, P $3.6 - 3.8 \times 10^{-2}$ Torr, t 5 min.) gave a brown oil (0.718 g), which was purified by Kugelrohr distillation to give ethyl 3-hydroxypyrrole-2-carboxylate **6.35** as a yellow solid (0.558 g, 85%); bp 72 °C (0.5 Torr); δ_H (360 MHz) 8.30 (1H, s, br), 7.74 (1H, s, br), 6.71 (1H, s, br), 5.87 (1H, t, 3J 2.9), 4.35 (2H, q, 3J 7.1) and 1.37 (3H, t, 3J 7.1); m/z 155 (53), 109 (100) and 81 (41). NMR data matches literature data.¹²¹

Deuteration Experiment

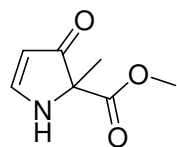
Ethyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-acetate (0.124 g) was heated in methanol-*d* (*ca.* 1cm³) and the solvent removed under high vacuum. Pyrolysis of the resulting solid (T_f 600 °C, T_i 200 °C, P $2.8 - 3.2 \times 10^{-2}$ Torr, t 8 min.) gave a brown oil. The compound was dissolved in deuteriated chloroform and the ¹H NMR spectrum recorded. By ¹H NMR spectroscopy, no incorporation of deuterium was observed in the product, and was predominantly N-deuteriated.

Methyl 2-[(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-propionate **6.40**



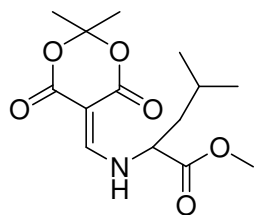
Using general method A, alanine methyl ester hydrochloride (0.349 g, 2.5 mmol) gave methyl 2-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-propionate **6.40** as a yellow solid (0.623 g, 97%); mp 125 – 126 °C (from ethanol); (Found C, 50.95; H, 5.75; N, 5.40. C₁₁H₁₅NO₆·0.1H₂O requires C, 51.0; H, 5.8; N, 5.4.) δ_H 9.74 (1H, br, s), 8.11 (1H, d, 3J 14.8), 4.23 (1H, pentet, 3J 7.3), 3.78 (3H, s), 1.67 (6H, s) and 1.59 (3H, d, 3J 7.3); δ_C 170.46 (quat), 165.15 (quat), 163.67 (quat), 158.29, 104.72 (quat), 85.73 (quat), 57.02, 53.06 (CH₃), 26.88 (2CH₃) and 18.74 (CH₃); m/z 257 (M⁺, 30%), 200 (30), 199 (13), 155 (18), 140 (100) and 96 (55).

Methyl 2-Methyl-3-oxo-2,3-dihydro-1H-pyrrole-2-carboxylate **6.43**



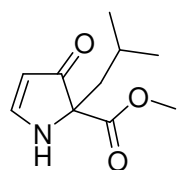
Pyrolysis of methyl 2-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-propionate **6.40** (w 0.306 g, T_f 600 °C, T_i 200 °C, P $2.3 - 2.4 \times 10^{-2}$ Torr, t 7 min.) gave an orange oil, which solidified on concentration from an acetone solution to give methyl 2-methyl-3-oxo-2,3-dihydro-1H-pyrrole-2-carboxylate **6.43** as an orange solid (0.182 g, 99%); mp 79 – 81 °C; (Found M^+ 155.05791, $C_7H_9NO_3$ requires 155.05769); δ_H 8.10 (1H, s), 6.65 (1H, br, s), 5.09 (1H, d, 3J 3.5), 3.71 (3H, s) and 1.57 (3H, s); δ_C 198.19 (quat), 168.28 (quat), 165.48, 97.63, 69.32 (quat), 53.16 (CH_3) and 20.99 (CH_3); m/z 155 (M^+ , 100%), 96 (87) and 112 (23).

Methyl 2-[(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-4-methyl-pentanoate **6.41**



Using general method A, leucine methyl ester hydrochloride (0.454 g, 2.5 mmol) gave methyl 2-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-4-methyl-pentanoate **6.41** as a yellow solid (0.687 g, 92%); mp 106 – 107 °C (from ethanol); (Found C, 56.4; H, 7.0; N, 4.75; $C_{14}H_{21}NO_6$ requires C, 56.2; H, 7.0, N; 4.75.); δ_H (500 MHz) 9.64 (1H, br, m), 8.08 (1H, d, 3J 14.5), 4.13 (1H, td, 3J 9.0, 4J 5.5), 3.80 (3H, s), 1.79 (2H, m), 1.71 (6H, s), 1.66 (1H, m), 0.97 (3H, d, 3J 7.0) and 0.96 (3H, d, 3J 7.0); δ_C (90 MHz) 170.34 (quat), 165.20 (quat), 163.63 (quat), 158.67, 104.76 (quat), 85.70 (quat), 60.70 (CH_3), 52.89, 41.53 (CH_2), 26.90 (CH_3), 26.82 (CH_3), 24.34, 22.50 (CH_3) and 21.41 (CH_3); m/z 299 (M^+ , 16%), 240 (15), 182 (100), 138 (18) and 96 (15).

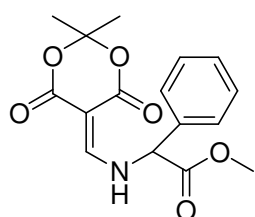
Methyl 2-Isobutyl-3-oxo-2,3-dihydro-1H-pyrrole-2-carboxylate **6.44**



Pyrolysis of methyl 2-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-4-methyl-pentanoate **6.41** (w 0.450 g, T_f 600 °C, T_i 170 °C, P $2.6 - 4.2 \times 10^{-2}$ Torr, t 24 min.) gave methyl 2-isobutyl-3-oxo-2,3-dihydro-1H-pyrrole-2-carboxylate **6.44** as an orange solid (0.240 g,

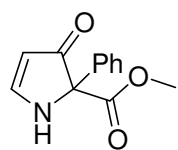
81%); mp 91 – 92 °C (Found M^+ 197.10460, $C_{10}H_{15}NO_3$ requires M^+ 197.10464); δ_H (500 MHz) 8.10 (1H, t, 3J 3.5), 6.11 (1H, br, s), 5.16 (1H, d, 3J 3.5), 3.76 (3H, s), 2.16 (1H, q, 3J 9.0), 1.73 (2H, m), 0.91 (3H, d, 3J 7.0) and 0.90 (3H, d, 3J 7.0); δ_C (90 MHz) 196.86 (quat), 168.02 (quat), 165.50, 99.02, 73.29 (quat), 53.11, 43.99 (CH_2), 25.39, 23.47 (CH_3) and 23.03 (CH_3); m/z 197 (M^+ , 11%), 154 (53), 141 (100), 126 (22), 109 (32) and 94 (69).

Methyl [(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-phenylacetate 6.42



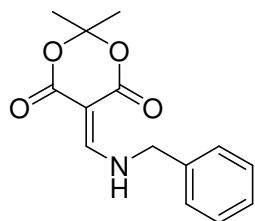
Using general method A, phenylglycine methyl ester hydrochloride (2.060 g, 10 mmol) gave methyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-phenyl-acetate **6.42** as a yellow solid (2.828 g, 89%); mp 178 – 181 °C (from ethanol); (Found C, 60.25; H, 5.05; N, 4.35. $C_{16}H_{17}NO_6$ requires C, 60.55; H, 5.35; N, 4.40.) δ_H 10.32 (1H, dd, 3J 14.5, 4J 5.8), 8.08 (1H, d, 3J 14.5), 7.45 – 7.32 (5H, m), 5.21 (1H, d, 3J 6.6), 3.80 (3H, s), 1.45 (3H, s) and 1.43 (3H, s); δ_C 168.75 (quat), 164.93 (quat), 163.46 (quat), 158.05, 134.21 (quat), 129.50, 129.41 (2CH), 127.14 (2CH), 104.68 (quat), 86.29 (quat), 64.52, 53.26 (CH_3) and 26.77 (2 CH_3); m/z 319 (M^+ , 31%), 260 (72), 202 (100) and 158 (100).

Methyl 3-Oxo-2-phenyl-2,3-dihydro-1H-pyrrole-2-carboxylate 6.45



Pyrolysis of methyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-phenyl-acetate **6.42** (w 1.0504 g, T_f 600 °C, T_i 220 °C, P 4.2 - 5.5 $\times 10^{-2}$ Torr, t 10 min.) gave methyl 3-oxo-2-phenyl-2,3-dihydro-1H-pyrrole-2-carboxylate **6.45** a brown solid (0.463 g, 65%); mp 177 – 179 °C (from toluene); (Found M^+ 217.07334, $C_{12}H_{11}NO_3$ requires 217.07334); δ_H (d_6 -DMSO) 9.41 (1H, br, s), 8.56 (1H, br, s), 7.57 – 7.35 (5H, m), 4.88 (1H, s) and 3.67 (3H, s); δ_C (d_6 -DMSO) 194.41 (quat), 167.04, 166.91 (quat), 135.13 (quat), 127.92 (2CH), 127.85, 126.31 (2CH), 94.09, 73.24 (quat) and 52.88 (CH_3), m/z 217 (M^+ , 17%), 185 (20), 130 (22), 105 (47) and 84 (100).

5-(Benzylamino-methylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **6.47**

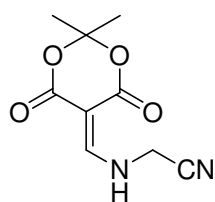


Using general method B, benzylamine (0.214 g, 2 mmol) gave 5-(benzylaminomethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **6.47** as a orange solid (0.549 g, quant.); mp 163 – 165 °C (from ethanol, lit.¹⁴² 166 - 167 °C); δ_H 9.75 (1H, br, s), 8.22 (1H, d, 3J 14.2), 7.44 – 7.36 (3H, m), 7.29 – 7.25 (2H, m), 4.61 (2H, d, 3J 6.1) and 1.70 (6H, s).

Pyrolysis of 5-(Benzylaminomethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **6.47**

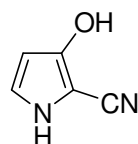
Pyrolysis of 5-(benzylaminomethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **6.47** (w 0.07 g, T_f 600 °C, T_i 200 °C, P $2.7 - 2.9 \times 10^{-2}$ Torr, t 7 min.) gave a yellow oil. 1H NMR spectroscopy showed no identifiable products and complex peaks.

[(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-acetonitrile **6.48**



Using general method A, aminoacetonitrile hydrogen sulfate (1.54 g, 10 mmol) gave [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-acetonitrile **6.48** as a yellow solid (1.86 g, 89%); mp 182 – 184 °C (from ethanol); (Found C, 51.75; H, 4.6; N, 13.0; $C_9H_{10}N_2O_4$ requires C, 51.45; H, 4.75; N, 13.35.) δ_H (d_6 -DMSO) 9.89 (1H, s), 8.34 (1H, s), 4.62 (2H, s) and 1.62 (6H, s); δ_C (d_6 -DMSO) 160.71, 117.03, 104.16, 85.77, 37.76 (CH_2) and 26.75 (2 CH_3), two carbonyl Cs not apparent due to restricted rotation; m/z 211 (M^+ , 71%), 210 (60), 153 (100), 109 (16) and 108 (45)

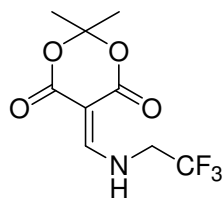
2-Hydroxy-3-cyanopyrrole **6.49**



Pyrolysis of [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-acetonitrile **6.48** (w 0.208 g, T_f 600 °C, T_i 200 °C, P $2.3 - 2.9 \times 10^{-2}$ Torr, t 10 min.) gave 2-hydroxy-3-cyanopyrrole **6.49** as an off white solid (0.0877 g, 74%); mp 92 – 94 °C; (Found M^+ 108.03181, $C_5H_4N_2O$ requires 108.03181); δ_H 11.23 (1H, br, s), 9.72 (1H, br, s), 6.78 (1H, d, 3J 2.5) and 5.65 (1H, m), δ_C 154.07 (quat), 123.07, 114.78 (quat), 97.85 and 85.11 (quat), m/z 108

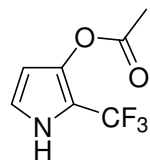
(M⁺, 100%).

2,2-Dimethyl-5-[(2,2,2-trifluoroethylamino)-methylene]-[1,3]dioxane-4,6-dione **6.50**



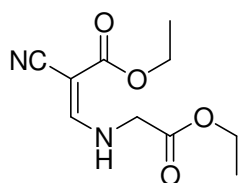
Using general method B, 2,2,2-trifluoroethylamine (1.98 g, 20 mmol) gave 2,2-dimethyl-5-[(2,2,2-trifluoroethylamino)-methylene]-[1,3]dioxane-4,6-dione **6.50** as an orange solid (4.82 g, 95%); mp 161 – 163 °C (from ethanol); (Found C, 42.85; H, 3.85; N, 5.45; C₉H₁₀FNO₄ requires C, 42.7; H, 3.95; N, 5.55.); δ_H 9.60 (1H, br, s), 8.17 (1H, d, 3J 13.7), 3.99 (2H, pentet, 3J 8.3) and 1.73 (6H, s); δ_C 165.16 (quat), 163.11 (quat), 160.92, 122.67 (quat, 1J 281.4), 105.18 (quat), 87.58 (quat), 50.42 (CH₂, 2J 33.7) and 26.88 (2CH₃); m/z 253 (M⁺, 81%), 196 (100), 167 (99), 151 (46) and 123 (32).

3-Acetoxy-2-trifluoromethylpyrrole **6.52**



Pyrolysis of 2,2-dimethyl-5-[(2,2,2-trifluoro-ethylamino)-methylene]-[1,3]dioxane-4,6-dione **6.50** (w 1.0126 g, T_f 600 °C, T_i 200 °C, P 3.0 – 3.2×10^{-2} Torr, t 22 min.) gave a orange oil. The oil was dissolved in DCM (20 cm³), triethylamine (0.7 cm³) and acetyl chloride (0.5 cm³) were added and the mixture stirred for 2.5 h at room temperature. The solution was washed twice with HCl (2M, 40 cm³) and NaHCO₃ (sat., 40 cm³). The organics were dried over MgSO₄ and the solution concentrated to give an orange oil. Kugelrohr distillation gave 3-acetoxy-2-trifluoromethylpyrrole **6.52** as a pale yellow oil (0.2208 g, 28%); bp 64 – 66 °C (2 Torr); (Found M⁺ 193.03477, C₇H₆F₃NO₂ requires 193.03451); δ_H (360 MHz) 8.69 (1H, br, s), 6.72 (1H, td, 3J 3.3, 4J 0.7), 6.16 (1H, td, 3J 3.2, 4J 0.7) and 2.28 (3H, s); δ_C (90 MHz) 164.84 (quat), 136.47 (quat), 120.51 (quat, 1J 264.8), 118.35, 103.81 and 20.45 (CH₃), one quat. not apparent; m/z 193 (M⁺, 30%), 151 (100) and 131 (63).

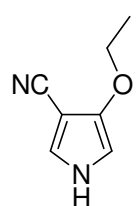
Ethyl 2-Cyano-3-(ethoxycarbonylmethylamino)-acrylate **6.53**



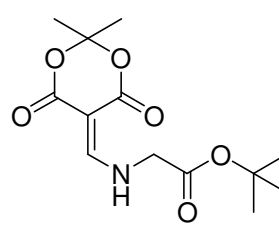
Using general method B, glycine ethyl ester hydrochloride (1.396

g, 10 mmol) and ethyl ethoxymethylenecyanoacetate (1.692 g, 10 mmol), in place of methoxymethylene Meldrum's acid, gave ethyl 2-cyano-3-(ethoxycarbonylmethylamino)-acrylate **6.53** as a off-white solid (1:2.5 mixture of *E/Z* isomers, 2.122 g, 94%); (Found C, 53.3; H, 5.9; N, 12.35. C₁₀H₁₄N₂O₆ requires C, 53.1; H, 6.25; N, 12.4); δ_H 9.08 (1H, br, s), 7.82 (1H, d, 3J 14.9), 7.28 (1H, d, 3J 13.7), 6.50 (1H, br, s), 4.29 – 4.16 (8H, m), 4.08 (1H, d, 3J 5.9), 4.06 (1H, d, 3J 6.0), 1.34 – 1.25 (12H, m); m/z 226 (M⁺, 60%), 181 (20), 153 (100), 125 (95), 107 (28) and 95 (15).

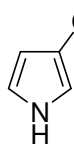
4-Ethoxy-1*H*-pyrrole-3-carbonitrile **6.54**

 Pyrolysis of ethyl 2-cyano-3-(ethoxycarbonylmethylamino)-acrylate **6.53** (w 0.550 g, T_f 600 °C, T_i 180 °C, P 3.4×10^{-2} Torr, t 12 min.) gave crude 4-ethoxy-1*H*-pyrrole-3-carbonitrile **6.54** as a dark brown oil (0.316 g, 96%). Attempts to purify the compound by distillation or column chromatography failed to yield any of the product; (Found M⁺ 136.06309, C₇H₈N₂O requires 136.06311) δ_H (360 MHz) 8.45 (1H, br, s), 7.05 (1H, dd, 3J 3.7, 4J 2.2), 6.27 (1H, t, 3J 2.4), 3.96 (2H, q, 3J 7.0), 1.40 (3H, t, 3J 7.0); δ_C (90 MHz) 148.80 (quat), 123.18, 115.14 (quat), 100.23, 84.58 (quat), 67.06 (CH₂) and 14.63 (CH₃); m/z 136 (M⁺, 43%).

tert-Butyl [(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-acetate **6.63**

 Using general method A, glycine *tert*-butyl ester hydrochloride (0.419 g, 2.5 mmol) gave *tert*-butyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-acetate **6.63** as a yellow solid (0.6343 g, 89%); mp 135 – 136 °C (from ethanol); (Found C, 54.95; H, 6.65; N, 4.95; C₁₃H₁₉NO₆ requires C, 54.75; H, 6.65; N, 4.9.); δ_H 9.61 (1H, br, m), 8.07 (1H, d, 3J 14.6), 4.09 (2H, d, 3J 5.8), 1.70 (6H, s) and 1.49 (9H, s); δ_C 166.07 (quat), 165.07 (quat), 165.53 (quat), 159.94, 104.61 (quat), 85.72 (quat), 83.65 (quat), 56.61 (CH₂), 27.74 (3CH₃) and 26.71 (2CH₃); m/z 285 (M⁺, 29%), 229 (14), 184 (23), 172 (32) and 126 (100).

3-Hydroxypyrrole 6.39



Pyrolysis of *tert*-butyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene methyl)-amino]-acetate **6.63** (w 0.0988 g, T_f 600 °C, T_i 200 °C, P 2.6 – 2.8 $\times 10^{-2}$ Torr, t 5 min.) gave 3-hydroxypyrrole **6.39** as an orange brown oil (55%, NMR yield based on a known cyclohexane standard);

Enol tautomer **6.39e** δ_H (360 MHz, d_6 -DMSO) 9.95 (1H, br, s), 7.79 (1H, br, s), 6.43 (1H, td, 3J 2.7, 4J 1.7), 6.16 (1H, td, 3J 2.7, 3J 2.4) and 5.61 (1H, td, 3J 2.4, 4J 1.7); δ_C (90 MHz, d_6 -DMSO) 143.72 (quat), 114.99, 100.51 and 98.19.

Keto tautomer **6.39k** δ_H (500 MHz, H₂O+D₂O) 8.27 (1H, m), 5.20 (1H, d, 3J 2.9) and 3.94 (2H, d, 4J 1.4); δ_C (125 MHz, H₂O+D₂O) 204.21 (quat), 170.83, 99.23 and 55.55 (CH₂)

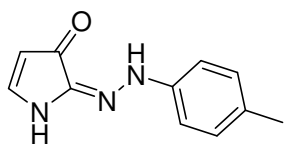
Reactions of 3-Hydroxypyrrole 6.39

Protonation in TFA

Using a fresh sample of 3-hydroxypyrrole, the oil was dissolved in TFA and the NMR spectra recorded. δ_H (TFA, 500 MHz) 8.92 (1H, s), 6.34 (1H, d, 3J 2.0) and 5.03 (2H, d, 3J 2.0); δ_C (TFA, 125 MHz) 189.23 (quat), 173.17, 100.17 and 54.83 (CH₂)

3-Hydroxypyrrole was also dissolved in *d*-TFA and the 1H NMR spectrum recorded. The peaks at δ_H = 6.34 and 5.03 ppm were not observed in this spectrum.

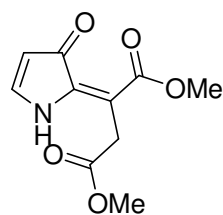
2-(*p*-Tolylhydrazono)-1,2-dihydro-pyrrol-3-one 6.70



Pyrolysis of *tert*-butyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene methyl)-amino]-acetate **6.63** (w 0.094 g, T_f 600 °C, T_i 200 °C, P 2.3 – 2.4 $\times 10^{-2}$ Torr, t 13 min.) gave a orange-brown oil, which was dissolved in DMF (2.5 cm³). *p*-Tolyldiazonium tetrafluoroborate (0.062 g, 0.33 mmol) was added and the resulting deep red solution

stirred for 20 min. The solution was diluted with water, extracted with ethyl acetate ($3 \times 20 \text{ cm}^3$) and the organic layers combined. The combined organics were washed with NaHCO_3 ($2 \times 20 \text{ cm}^3$), brine (20 cm^3), dried over MgSO_4 and the solvent removed to give a brown solid. Purification by column chromatography (hexane/ethyl acetate, 3:2 mixture) gave 2-(*p*-tolylhydrazono)-1,2-dihydro-pyrrol-3-one **6.70** as an orange-red solid (0.039 g, 56%); mp 188 – 190 °C (Found M^+ 201.08964, $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}$ requires M^+ 201.08966); δ_{H} (360 MHz) 7.66 (1H, t, 3J 3.6), 7.26–7.12 (4H, m), 5.53 (1H, d, 3J 3.6) and 2.32 (3H, s); δ_{C} (90 MHz) 177.88 (quat), 147.93, 140.10 (quat), 133.52 (quat), 132.60 (quat), 129.85 (2CH), 114.12 (2CH), 101.45 and 29.58 (CH_3); m/z 201 (M^+ , 100%) and 106 (26). λ_{max} (MeOH) 456.0 nm ($\epsilon = 11000 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$), 373.0 nm ($\epsilon = 7700 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$) and 260.0 ($\epsilon = 6400 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$)

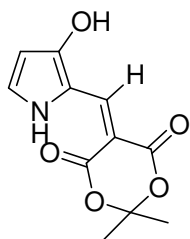
Dimethyl 2-[3-Oxo-1,3-dihydro-pyrrol-(2*E*)-ylidene]-succinate **6.76**



Pyrolysis of *tert*-butyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene methyl)-amino]-acetate **6.63** (w 0.0995 g, T_f 600, T_i 200 °C, P $2.4 - 2.6 \times 10^{-2}$ Torr, t 17 min.) gave a orange-brown oil, which was dissolved in DMF (2.5 cm^3). Dimethyl acetylenedicarboxylate (0.05 cm^3) was added and the solution stirred for 1 h at room temperature. The mixture was diluted with water and extracted with ethyl acetate ($3 \times 20 \text{ cm}^3$) and the organic layers combined. The combined organics were washed with NaHCO_3 ($2 \times 20 \text{ cm}^3$), brine (20 cm^3), dried over MgSO_4 and the solvent removed to give a brown solid. Purification by column chromatography (hexane/ethyl acetate, 3:2 mixture) gave dimethyl 2-[3-oxo-1,3-dihydro-pyrrol-(2*E*)-ylidene]-succinate **6.76** as a red solid (0.0324 g, 41%); mp 107 – 109 °C; (Found M^+ 225.06258, $\text{C}_{10}\text{H}_{11}\text{NO}_5$ requires 225.06317); δ_{H} (360 MHz) 9.03 (1H, br, s), 7.80 (1H, dd, 3J 3.9, 3J 3.4), 5.33 (1H, dd, 3J 3.9, 4J 1.9), 4.10 (2H, s), 3.82 (3H, s) and 3.71 (3H, s); δ_{C} (90 MHz) 190.03 (quat), 171.23 (quat), 168.64 (quat), 154.82, 138.41 (quat), 108.91 (quat), 101.88, 52.51 (CH_3), 51.93 (CH_3) and 29.38 (CH_2); m/z 225 (M^+ , 46%), 193 (100), 165 (39), 134 (22) and 106 (21).

5-(3-Hydroxy-1*H*-pyrrol-2-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione

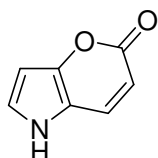
6.84



Pyrolysis of *tert*-butyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene methyl)-amino]-acetate **6.63** (w 0.108 g, T_f 600, T_i 200 °C, P $2.3 - 2.5 \times 10^{-2}$ Torr, t 23 min.) gave an orange-brown oil, which was dissolved in a mixture of DMF and triethylamine (10:1 mix, 4 cm³).

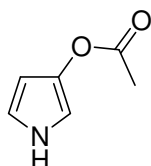
Methoxymethylene Meldrum's acid (0.067 g, 0.36 mmol) was added and the solution stirred for 1 h at room temperature. The mixture was diluted with water and extracted with ethyl acetate (3×20 cm³) and the organic layers combined. The combined organics were washed with 2M HCl, brine (2×20 cm³), dried over MgSO₄ and the solvent removed to give 5-(3-hydroxy-1*H*-pyrrol-2-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **6.84** as a brown solid (0.0547 g, 61%); mp 199 – 201 °C (decomp.); (Found M^+ 237.06274, C₁₁H₁₁NO₅ requires 237.06317); δ_H (d_6 -DMSO, 360 MHz) 11.64 (2H, br, s), 8.10 (1H, s), 7.63 (1H, t, 3J 2.7), 5.90 (1H, t, 3J 2.7) and 1.71 (6H, s); δ_C (d_6 -DMSO, 90 MHz) 164.30 (quat), 164.01 (quat), 162.17 (quat), 137.26, 133.89, 117.60 (quat), 103.15 (quat), 98.32, 92.74 (quat) and 26.57 (2CH₃), m/z 237 (M^+ , 40%), 179 (72), 135 (38) and 107 (100).

1*H*-Pyrano[3,2-*b*]pyrrol-5-one 6.85



Pyrolysis of 5-(3-hydroxy-1*H*-pyrrol-2-ylmethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione **6.84** (w 0.115 g, T_f 600 °C, T_i 220 °C, P $2.4 - 2.6 \times 10^{-2}$ Torr, t 24 min.) gave 1*H*-pyrano[3,2-*b*]pyrrol-5-one **6.85** as an orange-brown solid (0.0507 g, 77%); mp 155 – 157 °C; (Found M^+ 135.03123, C₇H₅NO₂ requires 135.03148); δ_H (360 MHz) 7.58 (1H, d, 3J 9.5), 7.05 (1H, t, 3J 2.9), 6.23 (1H, t, 3J 2.9) and 6.05 (1H, d, 3J 9.5); δ_C (90 MHz) 163.25 (quat), 147.84 (quat), 132.62, 123.27 (quat), 115.16, 107.13 and 97.65; m/z 135 (M^+ , 100%) and 107 (36).

3-Acetoxypyrrole 6.86



Pyrolysis of *tert*-butyl [(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene methyl)-amino]-acetate **6.63** (w 0.208 g, T_f 600, T_i 200 °C, P $2.9 - 3.2 \times 10^{-2}$ Torr, t 17 min.) gave an orange-brown oil, which was dissolved in

DMF (2.5 cm³). Triethylamine (0.5 cm³) and acetyl chloride (0.4 cm³) were added and the mixture stirred for 1 h at room temperature. The mixture was diluted with water, acidified and extracted with ethyl acetate three times. The combined organics were washed with HCl (2 M), sat. NaHCO₃ twice, then dried over MgSO₄ and the solution concentrated to give the crude material as a brown oil. The oil was purified by Kugelrohr distillation to give 3-acetoxypyrrole **6.86** as an orange oil (0.045 g, 49%); bp 88 – 90 °C (0.5 Torr); (Found M⁺ 125.04709, C₆H₇NO₂ requires 125.04713); δ_H (360 MHz) 8.03 (1H, br, s), 6.82 (1H, m), 6.63 (1H, td, ³J 3.0, ³J 2.3), 6.09 (1H, ddd, ³J 3.0, ⁴J 1.6) and 2.24 (3H, s); δ_C (90 MHz) 168.90 (quat), 137.40 (quat), 115.68, 107.01, 101.14 and 20.90 (CH₃); *m/z* 125 (M⁺, 37%) and 83 (100).

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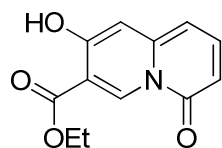
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**Appendix 1: Bond Lengths (Angstroms) and Angles (°) for Crystal Structure of
7-Carbethoxy-8-hydroxyquinolizin-4-one 4.127**



Bond Lengths

C1A C2A 1.381(4)

C1A C10A 1.387(4)

C1A H1A 0.9500

C2A C3A 1.392(4)

C2A H2A 0.9500

C3A C4A 1.403(4)

C3A H3A 0.9500

C4A O1A 1.256(3)

C4A N5A 1.438(4)

N5A C6A 1.370(4)

N5A C10A 1.396(3)

C6A C7A 1.359(4)

C6A H6A 0.9500

C7A C8A 1.435(4)

C7A C11A 1.497(4)

C8A O2A 1.334(3)

C8A C9A 1.371(4)

C9A C10A 1.404(4)

C9A H9A 0.9500

C11A O3A 1.194(4)

C11A O12A 1.357(4)

O12A C13A 1.459(3)

C13A C14A 1.502(3)

C13A H13A 0.9900

C13A H13B 0.9900

C14A H14A 0.9800

C14A H14B 0.9800

C14A H14C 0.9800
O2A H2A' 0.850(18)
C1B C2B 1.377(4)
C1B C10B 1.388(4)
C1B H1B 0.9500
C2B C3B 1.382(4)
C2B H2B 0.9500
C3B C4B 1.388(4)
C3B H3B 0.9500
C4B O1B 1.251(3)
C4B N5B 1.432(3)
N5B C6B 1.372(3)
N5B C10B 1.400(3)
C6B C7B 1.364(3)
C6B H6B 0.9500
C7B C8B 1.442(3)
C7B C11B 1.490(4)
C8B O2B 1.334(3)
C8B C9B 1.371(4)
C9B C10B 1.401(4)
C9B H9B 0.9500
C11B O3B 1.214(3)
C11B O12B 1.347(3)
O12B C13B 1.462(3)
C13B C14B 1.499(3)
C13B H13C 0.9900
C13B H13D 0.9900
C14B H14D 0.9800
C14B H14E 0.9800
C14B H14F 0.9800
O2B H2B' 0.863(18)

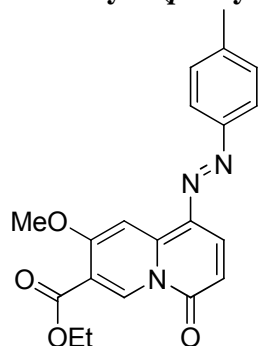
Bond Angles

C2A C1A C10A 120.4(3)
C2A C1A H1A 119.8
C10A C1A H1A 119.8
C1A C2A C3A 121.2(3)
C1A C2A H2A 119.4
C3A C2A H2A 119.4
C2A C3A C4A 121.2(3)
C2A C3A H3A 119.4
C4A C3A H3A 119.4
O1A C4A C3A 126.5(3)
O1A C4A N5A 117.5(3)
C3A C4A N5A 116.0(2)
C6A N5A C10A 119.9(2)
C6A N5A C4A 117.8(2)
C10A N5A C4A 122.4(2)
C7A C6A N5A 123.1(3)
C7A C6A H6A 118.5
N5A C6A H6A 118.5
C6A C7A C8A 118.7(3)
C6A C7A C11A 118.8(3)
C8A C7A C11A 122.5(2)
O2A C8A C9A 122.0(3)
O2A C8A C7A 120.1(2)
C9A C8A C7A 117.9(3)
C8A C9A C10A 122.9(3)
C8A C9A H9A 118.6
C10A C9A H9A 118.6
C1A C10A N5A 118.7(3)
C1A C10A C9A 123.7(3)
N5A C10A C9A 117.6(3)
O3A C11A O12A 124.1(3)
O3A C11A C7A 125.5(3)

O12A C11A C7A 110.4(2)
C11A O12A C13A 114.8(2)
O12A C13A C14A 107.5(2)
O12A C13A H13A 110.2
C14A C13A H13A 110.2
O12A C13A H13B 110.2
C14A C13A H13B 110.2
H13A C13A H13B 108.5
C13A C14A H14A 109.5
C13A C14A H14B 109.5
H14A C14A H14B 109.5
C13A C14A H14C 109.5
H14A C14A H14C 109.5
H14B C14A H14C 109.5
C8A O2A H2A' 109(2)
C2B C1B C10B 120.0(3)
C2B C1B H1B 120.0
C10B C1B H1B 120.0
C1B C2B C3B 120.9(3)
C1B C2B H2B 119.6
C3B C2B H2B 119.6
C2B C3B C4B 122.3(3)
C2B C3B H3B 118.9
C4B C3B H3B 118.9
O1B C4B C3B 127.5(2)
O1B C4B N5B 116.8(2)
C3B C4B N5B 115.7(2)
C6B N5B C10B 119.8(2)
C6B N5B C4B 117.93(19)
C10B N5B C4B 122.2(2)
C7B C6B N5B 122.9(2)
C7B C6B H6B 118.6
N5B C6B H6B 118.6

C6B C7B C8B 118.6(2)
C6B C7B C11B 118.3(2)
C8B C7B C11B 123.0(2)
O2B C8B C9B 122.4(2)
O2B C8B C7B 119.7(2)
C9B C8B C7B 117.9(2)
C8B C9B C10B 123.0(3)
C8B C9B H9B 118.5
C10B C9B H9B 118.5
C1B C10B N5B 118.7(2)
C1B C10B C9B 123.5(2)
N5B C10B C9B 117.8(2)
O3B C11B O12B 123.0(3)
O3B C11B C7B 125.2(2)
O12B C11B C7B 111.9(2)
C11B O12B C13B 115.48(19)
O12B C13B C14B 107.4(2)
O12B C13B H13C 110.2
C14B C13B H13C 110.2
O12B C13B H13D 110.2
C14B C13B H13D 110.2
H13C C13B H13D 108.5
C13B C14B H14D 109.5
C13B C14B H14E 109.5
H14D C14B H14E 109.5
C13B C14B H14F 109.5
H14D C14B H14F 109.5
H14E C14B H14F 109.5
C8B O2B H2B' 106(2)

Appendix 2: Bond Lengths (Angstroms) and Angles (°) for 7-Carbethoxy-8-methoxy-1-(*p*-tolylazo)quinolizin-4-one 4.179



Bond Lengths

O1 . C4 . 1.222(2)
O2 . C8 . 1.342(2)
O2 . C15 . 1.441(2)
O3 . C11 . 1.196(2)
O12 . C11 . 1.335(2)
O12 . C13 . 1.458(2)
N5 . C4 . 1.458(2)
N5 . C6 . 1.370(2)
N5 . C10 . 1.391(2)
N16 . N17 . 1.2692(19)
N16 . C1 . 1.398(2)
N17 . C18 . 1.423(2)
C1 . C2 . 1.404(2)
C1 . C10 . 1.402(2)
C2 . C3 . 1.356(2)
C2 . H21 . 0.941
C3 . C4 . 1.418(3)
C3 . H31 . 0.945
C6 . C7 . 1.355(2)
C6 . H61 . 0.941
C7 . C8 . 1.439(2)

C7 . C11 . 1.494(2)
C8 . C9 . 1.364(2)
C9 . C10 . 1.408(2)
C9 . H91 . 0.940
C13 . C14 . 1.499(2)
C13 . H131 . 0.963
C13 . H132 . 1.002
C14 . H141 . 0.964
C14 . H142 . 0.980
C14 . H143 . 0.974
C15 . H151 . 0.976
C15 . H152 . 0.986
C15 . H153 . 0.986
C18 . C19 . 1.396(2)
C18 . C24 . 1.393(2)
C19 . C20 . 1.374(2)
C19 . H191 . 0.942
C20 . C21 . 1.401(2)
C20 . H201 . 0.950
C21 . C22 . 1.504(2)
C21 . C23 . 1.388(2)
C22 . H221 . 0.950
C22 . H222 . 0.952
C22 . H223 . 0.970
C23 . C24 . 1.385(2)
C23 . H231 . 0.958
C24 . H241 . 0.960

Bond Angles

C8 . O2 . C15 . 117.17(14)

C11 . O12 . C13 . 116.12(14)

C4 . N5 . C6 . 116.33(14)

C4 . N5 . C10 . 123.58(14)

C6 . N5 . C10 . 120.09(15)

N17 . N16 . C1 . 114.72(15)

N16 . N17 . C18 . 113.39(14)

N16 . C1 . C2 . 125.24(16)

N16 . C1 . C10 . 115.41(15)

C2 . C1 . C10 . 119.32(16)

C1 . C2 . C3 . 122.00(17)

C1 . C2 . H21 . 118.0

C3 . C2 . H21 . 120.0

C2 . C3 . C4 . 122.60(17)

C2 . C3 . H31 . 119.8

C4 . C3 . H31 . 117.6

N5 . C4 . C3 . 114.09(15)

N5 . C4 . O1 . 117.87(16)

C3 . C4 . O1 . 128.04(17)

N5 . C6 . C7 . 123.30(15)

N5 . C6 . H61 . 117.3

C7 . C6 . H61 . 119.4

C6 . C7 . C8 . 117.84(16)

C6 . C7 . C11 . 118.71(15)

C8 . C7 . C11 . 123.43(16)

C7 . C8 . O2 . 116.71(15)

C7 . C8 . C9 . 118.91(16)

O2 . C8 . C9 . 124.38(15)

C8 . C9 . C10 . 122.24(16)

C8 . C9 . H91 . 120.3

C10 . C9 . H91 . 117.4

C9 . C10 . C1 . 124.02(16)

C9 . C10 . N5 . 117.61(15)

C1 . C10 . N5 . 118.36(16)

C7 . C11 . O12 . 111.19(15)

C7 . C11 . O3 . 125.12(16)

O12 . C11 . O3 . 123.67(16)

O12 . C13 . C14 . 106.77(14)

O12 . C13 . H131 . 108.1

C14 . C13 . H131 . 110.5

O12 . C13 . H132 . 110.1

C14 . C13 . H132 . 112.6

H131 . C13 . H132 . 108.6

C13 . C14 . H141 . 109.7

C13 . C14 . H142 . 108.6

H141 . C14 . H142 . 108.6

C13 . C14 . H143 . 110.7

H141 . C14 . H143 . 110.3

H142 . C14 . H143 . 109.0

O2 . C15 . H151 . 106.0

O2 . C15 . H152 . 108.5

H151 . C15 . H152 . 111.2

O2 . C15 . H153 . 108.1

H151 . C15 . H153 . 110.3

H152 . C15 . H153 . 112.4

N17 . C18 . C19 . 124.86(15)

N17 . C18 . C24 . 115.71(16)

C19 . C18 . C24 . 119.35(16)

C18 . C19 . C20 . 119.91(16)

C18 . C19 . H191 . 120.3

C20 . C19 . H191 . 119.8

C19 . C20 . C21 . 121.46(17)

C19 . C20 . H201 . 119.2

C21 . C20 . H201 . 119.3

C20 . C21 . C22 . 120.54(17)

C20 . C21 . C23 . 117.96(16)

C22 . C21 . C23 . 121.50(16)

C21 . C22 . H221 . 111.2

C21 . C22 . H222 . 109.5

H221 . C22 . H222 . 107.9

C21 . C22 . H223 . 111.0

H221 . C22 . H223 . 109.8

H222 . C22 . H223 . 107.3

C21 . C23 . C24 . 121.27(16)

C21 . C23 . H231 . 118.9

C24 . C23 . H231 . 119.8

C18 . C24 . C23 . 119.98(17)

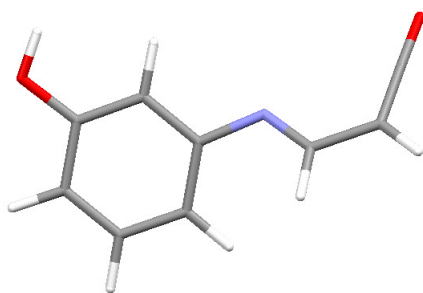
C18 . C24 . H241 . 119.6

C23 . C24 . H241 . 120.4

Appendix 3: Representative Computational Data

This section contains the Cartesian coordinates, energies and negative frequencies for the energy surface shown on page 178 (Figure 4.9). All structures and energies were calculated at B3LYP/6-31G** level, using Gaussian 03 and energies are quoted in Hartrees (HF). Transition states are optimized to a first order state using the switch “Opt=(TS,CalcFC,NoEigenTest)”.

Hydroxyquinolin-4-one Ketene



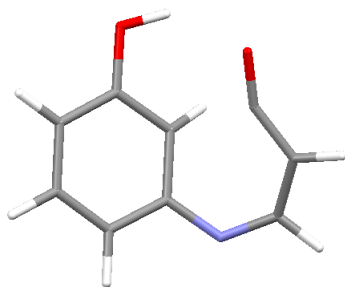
Energy = -552.3332334 HF

Cartesian Coordinates

C	2.285158	1.637601	-0.327590
C	0.898926	1.482594	-0.287456
C	0.348508	0.209592	-0.060356
C	1.205389	-0.891853	0.093038
C	2.588687	-0.718449	0.062292
C	3.138422	0.552762	-0.147051
C	-1.819705	0.811809	0.523155
N	-1.034181	-0.042951	-0.024817
C	-3.263937	0.651579	0.529639
C	-3.855166	-0.371386	-0.084215
O	-4.391612	-1.255986	-0.616015
O	3.460520	-1.759324	0.225156
H	0.765865	-1.874142	0.246149
H	4.216687	0.662732	-0.181089
H	-1.453873	1.714437	1.030336

H	0.246672	2.329882	-0.471467
H	-3.909143	1.358784	1.037982
H	2.707771	2.621071	-0.512629
H	2.956340	-2.575125	0.342578

5-Hydroxyquinolin-4-one 1st Transition State



Total Energy: -552.317412 HF

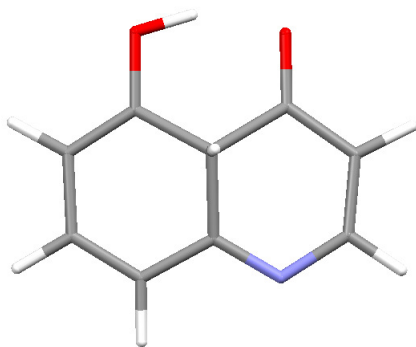
Cartesian Coordinates

C	-1.395333	1.191400	-0.379344
C	-2.430589	0.309826	-0.337655
C	-2.388924	-1.036465	0.164925
N	-1.361675	-1.783634	0.452827
C	-0.107831	-1.231845	0.289975
C	0.130610	0.139072	0.611401
O	-1.006902	2.306538	-0.563030
C	0.929984	-1.993491	-0.262462
C	2.160617	-1.393365	-0.522038
C	2.398969	-0.035996	-0.271583
C	1.388536	0.729419	0.298435
O	1.603442	2.040120	0.539525
H	-3.356203	0.670289	-0.777721
H	-3.363932	-1.511979	0.280256
H	-0.431926	0.570990	1.437192
H	3.347014	0.430006	-0.514172
H	2.955207	-1.989176	-0.962522
H	0.744412	-3.033928	-0.502786
H	0.748597	2.504646	0.508072

Calculated Negative Frequencies

-317.6110

5-Hydroxyquinolin-4-one 1st Intermediate

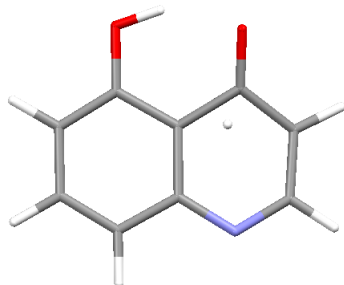


Energy : -552.344951 HF

Cartesian Coordinates

C	-1.287544	0.916198	0.040213
C	0.011727	0.212733	0.340234
C	0.049326	-1.281188	0.076011
C	-1.192990	-1.953985	-0.018170
C	-2.367916	-1.237344	-0.108013
C	-2.435423	0.181665	-0.110192
C	1.295047	0.974337	-0.015249
C	2.461759	0.156631	-0.085537
C	2.341236	-1.216871	-0.051664
N	1.192429	-1.945295	0.001346
O	1.268787	2.214757	-0.132549
O	-1.287637	2.240830	0.020370
H	-1.178784	-3.035232	-0.091230
H	-3.300051	-1.784483	-0.223464
H	-3.376771	0.695147	-0.267488
H	3.422437	0.633858	-0.241788
H	3.246665	-1.818728	-0.116936
H	0.062838	0.239927	1.450404
H	-0.323865	2.528812	-0.027278

5-Hydroxyquinolin-4-one 2nd Transition State



Energy = --552.2935978

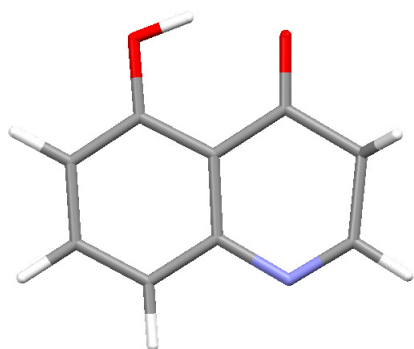
Cartesian Coordinates

C	1.249725	0.913531	0.096249
C	-0.009298	0.207607	0.053821
C	-0.018280	-1.238647	-0.105148
C	1.218555	-1.922725	-0.128711
C	2.398617	-1.215138	-0.018765
C	2.428055	0.191874	0.088870
C	-1.279774	0.977165	-0.164450
C	-2.374842	0.127404	0.292922
C	-2.289811	-1.278808	0.100877
N	-1.178146	-1.947966	-0.137340
O	-1.322621	2.189084	-0.398846
O	1.270745	2.255091	0.150216
H	1.198823	-3.002465	-0.217195
H	3.368798	0.729546	0.131099
H	-3.332856	0.592001	0.506111
H	-3.201151	-1.867837	0.194210
H	-1.012903	0.235820	1.140155
H	3.342783	-1.751955	-0.026579
H	0.360855	2.573670	-0.071377

Calculated Negative Frequencies

-1568.9237

5-Hydroxyquinolin-4-one 2nd Intermediate

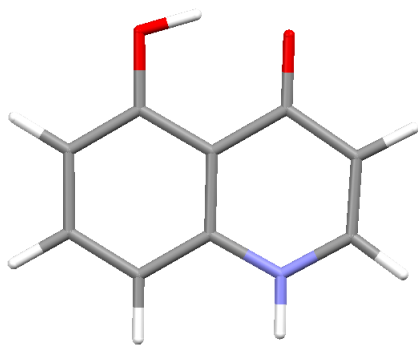


Energy = -552.3862177

Cartesian Coordinates

C	-1.304675	0.866304	0.000019
C	-0.041309	0.218766	-0.000139
C	0.023221	-1.203937	-0.000639
C	-1.151468	-1.948035	0.000075
C	-2.389881	-1.290645	0.001375
C	-2.478778	0.094774	0.001215
C	1.178393	1.003426	-0.000379
C	2.486127	0.237443	0.005484
C	2.339744	-1.258972	-0.001801
N	1.240773	-1.915483	-0.003382
O	1.185485	2.245460	-0.003227
O	-1.407280	2.200162	-0.000488
H	-1.081220	-3.029441	-0.000714
H	-3.434819	0.606322	0.001829
H	3.086129	0.562633	-0.856132
H	3.264439	-1.840720	-0.004991
H	3.069474	0.552735	0.882502
H	-3.303297	-1.878708	0.002087
H	-0.479999	2.555849	-0.002451

5-Hydroxyquinolin-4-one

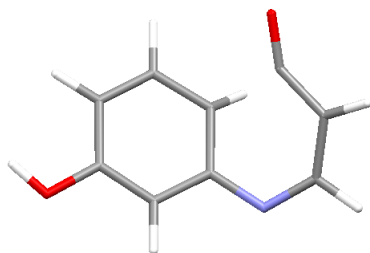


Energy = -552.4084462 HF

Cartesian Coordinates

C	1.206675	0.989977	0.000000
C	0.000000	0.230390	0.000000
C	0.085260	-1.181690	0.000000
C	1.324911	-1.834887	0.000000
C	2.482979	-1.062951	0.000000
C	2.440489	0.331878	0.000000
C	-1.296888	0.909664	0.000000
C	-2.462279	0.051036	0.000000
C	-2.323177	-1.301752	0.000000
N	-1.099645	-1.903845	0.000000
O	-1.384008	2.162160	0.000000
O	1.165173	2.325308	0.000000
H	1.374334	-2.919709	0.000000
H	3.448116	-1.561295	0.000000
H	3.346975	0.926335	0.000000
H	-3.443460	0.508514	0.000000
H	-3.173165	-1.975534	0.000000
H	-1.043777	-2.911114	0.000000
H	0.191355	2.569984	0.000000

7-Hydroxyquinolin-4-one 1st Transition State



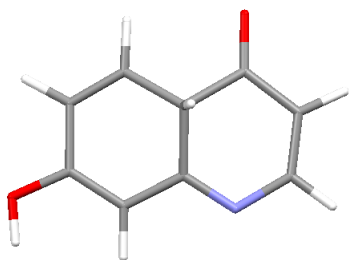
Energy = -552.3114064 HF

Cartesian Coordinates

C	-1.988732	0.877077	-0.336974
C	-2.650074	-0.333775	-0.415228
C	-2.131011	-1.582745	0.010829
N	-0.900413	-1.897980	0.352647
C	0.018986	-0.887045	0.364374
C	-0.347854	0.453978	0.732405
O	-2.119351	2.047197	-0.518814
C	1.330443	-1.151666	-0.067823
C	2.251847	-0.118692	-0.156932
C	1.903037	1.216165	0.195937
C	0.641267	1.482040	0.657012
O	3.492896	-0.420396	-0.607133
H	-3.593812	-0.312257	-0.952118
H	-2.833167	-2.417274	-0.009533
H	-1.082593	0.549066	1.533475
H	0.370130	2.492051	0.948194
H	2.645920	2.005787	0.111656
H	1.606938	-2.158563	-0.356759
H	4.033662	0.380621	-0.637462

Calculated Negative Frequencies

7-Hydroxyquinolin-4-one 1st Intermediate

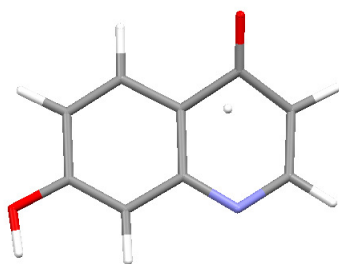


Energy: -552.333362 HF

Cartesian Coordinates

C	-0.539188	1.584069	0.133370
C	0.448705	0.500913	0.396739
C	-0.024580	-0.910414	0.120669
C	-1.431892	-1.129944	0.034705
C	-2.299072	-0.070847	-0.043117
C	-1.844022	1.306846	-0.038013
C	1.896945	0.802056	-0.045561
C	2.722200	-0.386445	-0.114461
C	2.149600	-1.627947	-0.060706
N	0.807254	-1.922167	0.013339
O	2.273524	1.954259	-0.217827
O	-3.637152	-0.210006	-0.172569
H	-1.777011	-2.156416	-0.053385
H	-2.586906	2.080278	-0.201543
H	3.783444	-0.265106	-0.302590
H	2.788033	-2.506566	-0.137469
H	0.598050	0.492154	1.499592
H	-0.153761	2.597789	0.112942
H	-3.865788	-1.150710	-0.189513

7-Hydroxyquinolin-4-one 2nd Transition State

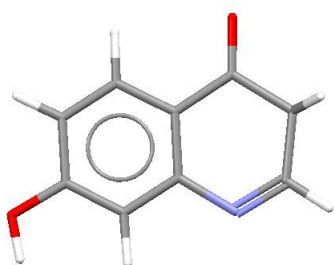


Energy = -552.2853234 HF

Cartesian Coordinates

C	0.516166	1.559854	0.224709
C	-0.443272	0.500187	0.121190
C	0.029401	-0.854637	-0.105127
C	1.427346	-1.085890	-0.163146
C	2.314841	-0.042509	-0.010349
C	1.854373	1.294558	0.190858
C	-1.895443	0.813286	-0.164909
C	-2.626764	-0.366534	0.338725
C	-2.085320	-1.657207	0.102284
N	-0.815072	-1.914028	-0.168532
O	-2.340368	1.903749	-0.467827
O	3.663620	-0.197122	-0.039220
H	1.763132	-2.107995	-0.312341
H	2.596410	2.080590	0.283038
H	-3.685213	-0.265112	0.563543
H	-2.743388	-2.520947	0.190279
H	0.142876	2.574751	0.313800
H	3.878025	-1.127293	-0.195203
H	-1.380318	0.144540	1.187573

7-Hydroxyquinolin-4-one 2nd Intermediate

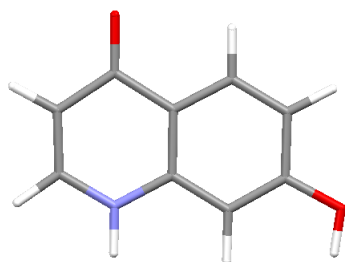


Energy = -552.3738415 HF

Cartesian Coordinates

C	-0.568452	1.568812	0.000257
C	0.385404	0.539105	0.000035
C	-0.049211	-0.807062	-0.000359
C	-1.417189	-1.090285	-0.000338
C	-2.350597	-0.050263	0.000153
C	-1.924723	1.288962	0.000439
C	1.823495	0.851100	-0.000205
C	2.760092	-0.353614	0.002206
C	2.086043	-1.696556	-0.000360
N	0.824703	-1.917162	-0.001246
O	2.269820	1.990271	-0.001736
O	-3.691216	-0.273831	0.000322
H	-1.728014	-2.131382	-0.000791
H	-2.670498	2.076240	0.000775
H	3.431855	-0.274760	-0.864138
H	2.738296	-2.573676	-0.001241
H	-0.209489	2.592843	0.000376
H	3.425022	-0.275693	0.874011
H	-3.858093	-1.226149	0.000065

7-Hydroxyquinolin-4-one

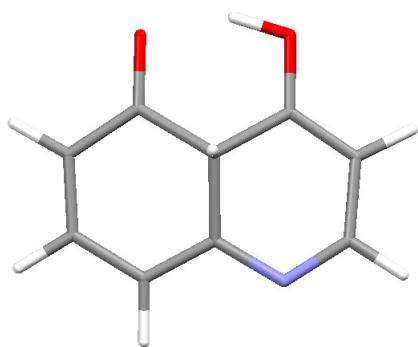


Energy = -552.391111 HF

Cartesian Coordinates

C	1.388008	0.905405	0.000000
C	0.000000	0.677159	0.000000
C	-0.456513	-0.657721	0.000000
C	0.454114	-1.729232	0.000000
C	1.819159	-1.463412	0.000000
C	2.293714	-0.136435	0.000000
C	-0.948050	1.817056	0.000000
C	-2.357740	1.432260	0.000000
C	-2.733153	0.129348	0.000000
N	-1.821008	-0.894837	0.000000
O	-0.568097	2.991145	0.000000
O	2.758235	-2.450717	0.000000
H	0.090914	-2.755333	0.000000
H	3.364656	0.033140	0.000000
H	-3.102524	2.218672	0.000000
H	-3.772609	-0.181592	0.000000
H	-2.149091	-1.848061	0.000000
H	1.715633	1.939783	0.000000
H	2.321754	-3.312743	0.000000

8-Hydroxyquinolizinone Intermediate

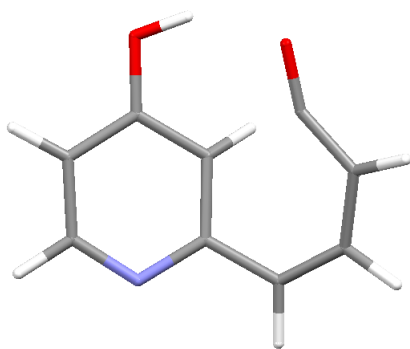


Energy: -552.3448582 HF

Cartesian Coordinates

C	-1.283225	0.978730	0.037932
C	0.006122	0.212865	0.367538
C	0.018715	-1.278021	0.088718
C	-1.187991	-1.921682	-0.046106
C	-2.400026	-1.181614	-0.116780
C	-2.473937	0.191986	-0.076576
C	1.295915	0.907801	-0.001211
C	2.421409	0.145182	-0.148250
C	2.306411	-1.273281	-0.056161
N	1.195861	-1.973198	0.037960
O	1.302333	2.226272	-0.079631
O	-1.250420	2.224164	-0.034019
H	-1.192030	-3.000230	-0.152433
H	-3.322757	-1.741059	-0.252167
H	-3.410212	0.718652	-0.223734
H	3.378803	0.612462	-0.345207
H	3.225499	-1.858143	-0.102087
H	-0.023972	0.264367	1.477252
H	0.337961	2.521050	-0.052767

8-Hydroxyquinolizinone Transition State



Energy = -552.3114382 HF

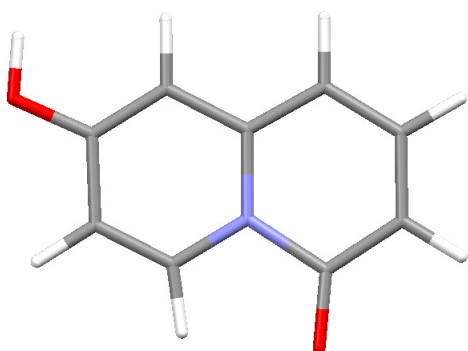
Cartesian Coordinates

C	-1.584898	1.106057	-0.260279
C	-2.514730	0.110510	-0.255918
C	-2.319105	-1.275382	0.049072
C	-1.148487	-1.937565	0.298975
C	0.115119	-1.259276	0.243947
C	0.142004	0.142142	0.523870
O	-1.334252	2.274142	-0.337494
N	1.209595	-1.936632	-0.157944
C	2.313906	-1.219839	-0.386850
C	2.417312	0.173161	-0.290328
C	1.317435	0.871096	0.198236
O	1.385293	2.201289	0.365986
H	-3.465200	0.416331	-0.689454
H	-3.225136	-1.873769	-0.006377
H	-0.471826	0.496423	1.351586
H	3.329201	0.696471	-0.552448
H	3.188265	-1.791550	-0.694584
H	0.479726	2.563410	0.380720
H	-1.141855	-3.019772	0.363891

Calculated Negative Frequencies

-395.6430

8-Hydroxyquinolizinone



Energy = -552.3815258 HF

Cartesian Coordinates

C	1.427448	1.111666	0.000008
C	0.020254	0.886037	-0.000104
N	-0.418614	-0.442204	-0.000189
C	0.485465	-1.481020	-0.000107
C	1.826430	-1.273382	0.000029
C	2.315988	0.066843	0.000074
C	-0.926002	1.906199	-0.000117
C	-2.288495	1.584938	0.000011
C	-2.735147	0.279607	0.000008
C	-1.838053	-0.827172	-0.000482
O	3.663808	0.209429	0.000192
O	-2.113981	-2.024319	0.000400
H	1.769757	2.142159	0.000058
H	0.014265	-2.454995	-0.000211
H	2.520801	-2.103901	0.000068
H	-0.585163	2.934074	-0.000043
H	-3.017680	2.390998	0.000227
H	-3.789958	0.034779	0.000350
H	3.892328	1.149141	0.000209